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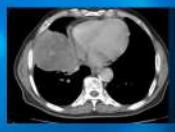

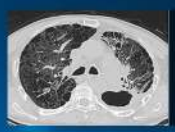

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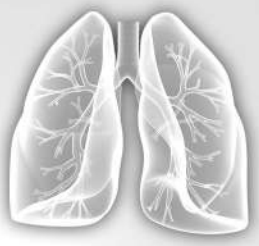

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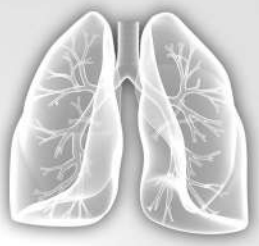

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Chylothorax as Part of Lymphatic Cystic Malformations Developing in Adulthood

Yetişkinlikte Ortaya Çıkan Lenfatik Kistik Malformasyonların Bir Parçası Olarak Şilotoraks

Meryem Karhate Andaloussi, Lamiyae Senhaji, Bouchra Amara, Mounia Serraj

Abstract

Lymphatic cystic malformations (LCMs) are rare, benign anomalies that, despite being congenital, may not be diagnosed until adulthood. LCMs that affect the skin, mucous membranes or underlying soft tissues are referred to as superficial LCMs, while those involving deeper organs are termed deep LCMs. Genetically, LCMs result from the activation of a somatic postzygotic mutation in the PIK3CA gene that disrupts and activates the PI3K/ATK/mTOR cell-signaling pathway involved in lymphangiogenesis, which predicts a good response to mTOR inhibitors. We report here on the case of a 23-year-old patient who presented in 2010 with both superficial and deep LCMs, and whose symptoms regress following treatment with mTOR inhibitors.

Keywords: *Lymphatic malformations, chylothorax, MTOR inhibitor.*

Öz

Lenfatik kistik malformasyonlar (LCM'ler) nadir görülen, iyi huylu malformasyonlardır ve konjenital olmalarına rağmen tanı yetişkinlikte konulabilir. LCM'ler cildi, mukoz membranları veya cilt altı yumuşak dokuları tutabilir ve bu durumda yüzeysel LCM'ler olarak adlandırılır veya altta yatan organları tutabilir ve bu durumda derin LCM'ler olarak adlandırılır. Genetik açıdan bakıldığında, LCM'ler lenfanjiyogenezde rol oynayan PI3K/ATK/MTOR hücre sinyal yolağını bozan ve aktive eden PIK3CA geninin aktive edici somatik postzinotik mutasyonu ile ilişkilidir ve bu da mTOR inhibitörüne iyi bir yanıt alınmasını öngörmektedir. Bu makalede, 2010 yılından beri yüzeysel ve derin LCM'leri olduğu bildirilen ve mTOR inhibitörü ile tedavi edilerek semptomları gerileyen 23 yaşında bir hasta sunulmuştur.

Anahtar Kelimeler: *Lenfatik malformasyonlar, şilotoraks, MTOR inhibitörü.*

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Lymphatic cystic malformations (LCMs) are rare, benign malformations that can be life-threatening due to their local invasiveness. Males and females, as well as people of different ethnic origins, are affected equally. Although congenital, they are not always apparent at birth, and while diagnosis can be delayed until adulthood, around 90 percent of cases are diagnosed before the age of 5 years. Genetically, LCMs are linked to the activation of a somatic post-zygotic mutation in the PIK3CA gene that disrupts and activates the PI3K/AKT/mTOR cell-signaling pathway that plays a role in lymphangiogenesis, suggesting a favorable response to mTOR inhibitors (1-3). In the absence of consensus on the optimum treatment, we present a case who presented with both superficial and deep MCLs and who responded well to treatment with mTOR inhibitors.

CASE

We present the case of a 23-year-old patient with a subcutaneous lesion in the right inguinal fold that had been developing since 2010. This lesion exhibited a rapid increase in both size and depth, extending to the scrotum and contralateral inguinal fold, and accompanied by signs of superinfection. This prompted the patient to consult a urologist in May 2018, when a pelvic CT scan revealed a tumoral process involving the superficial soft tissues of the anteromedial aspect of the right thigh, along with osteolytic bone lesions in the pelvis. Neoplastic origin was initially suspected, but a bone scan conducted in June 2018 revealed no bone fixation.

The patient was lost to follow-up between 2018 and 2020, but was reassessed on September 2020, when a pelvic MRI (Figure 1) revealed an infiltrative process characterized by poorly defined microcystic structures, situated supraponeuratically and with subaponeurotic extension affecting the bilateral inguinal regions. The infiltrate extended superiorly through the obturator region to the pelvic floor, posteriorly infiltrating the presacral space and retroperitoneum, and inferiorly to the right adductor fossa and the base of the scrotum, and ultimately infiltrating the perineal region. A distinct mass measuring 60 x 83 mm was identified on the medial aspect of the right thigh. Imaging revealed hyperintensity on the T2 and STIR sequences and isointensity on T1 with discreet and heterogeneous enhancement following contrast administration. This infiltration involved the external iliac and inferior mesenteric vessels, both of which remained patent. Additionally, multiple osteolytic lesions were identified in the sacrum and bilaterally in the iliac wings that were not enhanced by contrast. The findings suggested a lymphatic malformation, while the observed enhancements pointed to superinfection.

Figure 1: MRI: Infiltrate made up of microcystic structures, involving the bilateral inguinal regions, and infiltrating the perineal region, creating a true mass on the medial aspect of the right thigh measuring 60 x 83 mm. The whole is described as hypersignal T2 and STIR, iso-signal T1, discreetly and heterogeneously enhanced after contrast; the infiltration encompassed the external iliac and inferior mesenteric vessels, which are permeable. Multiple osteolytic lesions involving the sacrum and iliac wings bilaterally, not enhanced with contrast

Figure 2: Swelling at the root of the right thigh

A diagnosis of inguinoscrotal lymphangioma was established that was treated with sclerotherapy and bleomycin, leading to a slight regression of the condition. Treatment involving an mTOR inhibitor was indicated, but the patient declined to initiate this treatment and was again lost to follow-up.

The patient presented to the emergency department 1 year later with symptoms that had persisted for 1 month, including pelvic swelling and severe bone pain in the left hip radiating down the left leg that had become bilateral and debilitating. The pain rendered sitting impossible and the patient could stand only with assistance, while there were no accompanying sensory or motor deficits. The patient's condition had worsened 5 days before the consultation with the acute onset of dyspnea, dry cough with chest pain, a fever of 40°C and asthenia.

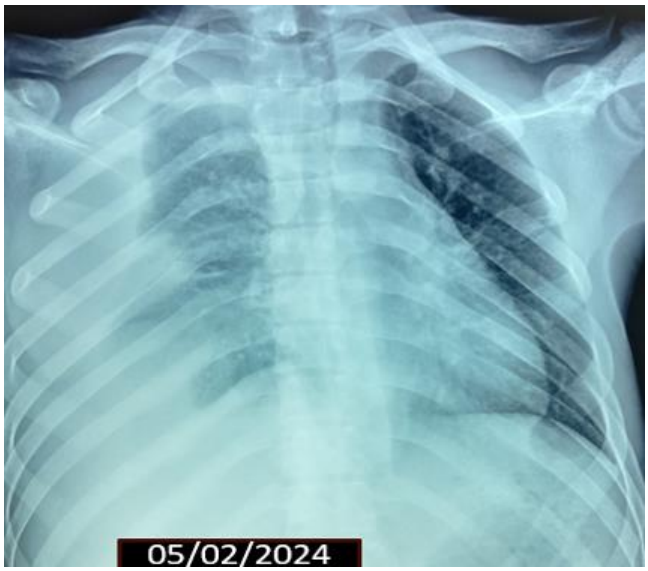

Figure 3: Front chest X-ray showing encysted pleurisy

A clinical examination revealed polypnea and 94% oxygen saturation, while a pleuropulmonary assessment indicated the presence of liquid effusion syndrome in the right thoracic hemithorax. A soft, non-tender swelling was identified upon palpation that was characterized by multiple flesh-colored cysts located in the right inguinal region (5 cm), at the root of the right thigh (7 cm), and on the underside of the right scrotum (6 cm) and perineum (Figure 2).

A frontal thoracic X-ray revealed an appearance consistent with encysted pleurisy (Figure 3).

In a thoraco-abdomino-pelvic CT scan performed in February 2024 (Figure 4), the supra- and subaponeurotic tissue infiltration was found to have increased in size and to have extended intra- and sub-peritoneally, associated to an appearance of a pleural localization, and the bone involvement identified during previous imaging was noted to have worsened. The combined findings pointed to multifocal lymphangiomatosis with a malformed appearance.

A thoracic MRI was performed to further investigate the thoracic duct revealing ectasia of the axillary and right intercostal lymphatic ducts characterized by hyperintensity on T2-weighted images, consistent with dilated lymphatic vessels. Additionally, a tubular structure was noted in the posterior mediastinum along the lateral border of the aorta, indicating an abnormal dilation of the thoracic duct. Furthermore, a significant pleural effusion was noted on the left and a moderate effusion on the right with heterogeneous hyperintensity on T2-weighted images, suggestive of chylothorax (Figure 5).

Pleural puncture revealed a milky fluid (Figure 6) that was identified as lymphocytic exudate by biochemical and cytobacteriological analyses with a triglyceride level of 8.47 g/L and a positive chylomicron assay. No microbial growth was detected in the culture, confirming the diagnosis of chylothorax.

The patient underwent drainage and was placed on a low-fat diet. The drain produced an average of 1200 cc of lactescent fluid per day. A multidisciplinary consultation deemed surgery to be inappropriate due to the high risk of recurrence, and the decision was made to initiate medical treatment with the Everolimus mTOR inhibitor at a dosage of 10 mg/day (off-label indication), with the possibility of subsequent surgery depending on clinical progress.

An assessment following 6 months of treatment revealed bilateral regression of pleurisy, leading to the cessation of drainage after first 3 months of treatment, as well as a reduction in the size of the inguinal swelling and resolution of pain.

DISCUSSION

Lymphatic Cystic Malformations (LCMs) are benign, slow-flowing anomalies characterized by abnormal cystic dilatations, the etiology of which remains poorly understood. LCMs that affect the skin, mucous membranes or underlying soft tissues are classified as superficial LCMs, while those that involve deeper organs are referred to as deep LCMs. Superficial LCMs are more prevalent than deep LCMs. LCMs were first described by Rodenber back in 1828, however, there have been few studies since then contributing to epidemiological knowledge of the condition (1,4).

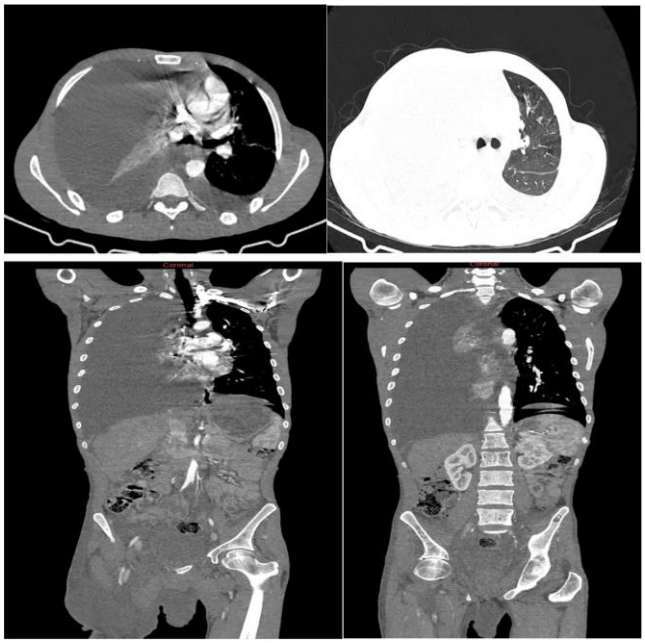

Figure 4: CT scan showing supra- and subaponeurotic tissue infiltration with intra- and subperitoneal extension, pleural localization and worsening bone involvement

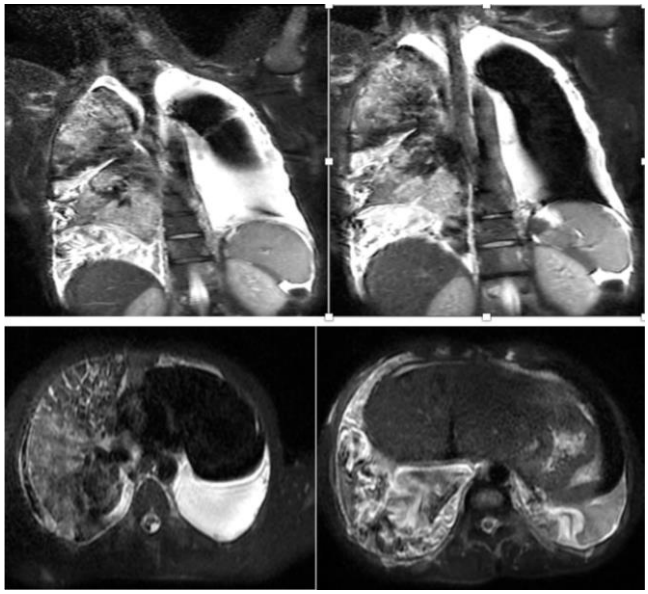

Figure 5: Ectasia of the intrapulmonary lymphatic sector and lymph node areas, associated with thoracic duct dilatation and chylothorax in the context of lymphangiomatosis

Clinically, superficial LCMs may present as round or lobulated subcutaneous masses several centimeters in diameter, exhibiting normal skin coloration and a soft or firm, elastic consistency. The most common anatomical locations include the neck, proximal limbs, axilla and inguinal regions, and approximately 90 percent of cases are diagnosed before the age of 5 years. In the case presented here, no diagnosis was made until adulthood.

Deep LCMs can affect all lymphatic territories and can involve single or, more commonly, multiple organs, with thoracic involvement being the most prevalent. The affected structures can include the lungs, mediastinum, heart, pleura, thoracic duct and chest wall. The prognosis of deep LCMs varies depending on the organ involved, with hepatic, splenic and thoracic involvement being associated with poorer prognoses due to their diffuse nature and limited surgical accessibility. A review of 53 cases of thoracic involvement in LCMs conducted by Alvarez et al. reported a worse prognosis in those under the age of 16 years when compared to older patients, with respective mortality rates of 39% and 0% (5-7). Thoracic involvement in particular is linked to a poor prognosis (4).

Bone involvement in LCMs is exceptionally rare, with only 16 cases documented in the literature reporting an association between chylothorax and bone involvement. Chylothorax and bone lesions were identified concurrently in 13 of these recorded cases, while in the remaining cases the bone involvement manifested as pain and preceded the development of chylothorax, with delays ranging from 6 months to 5 years (9).

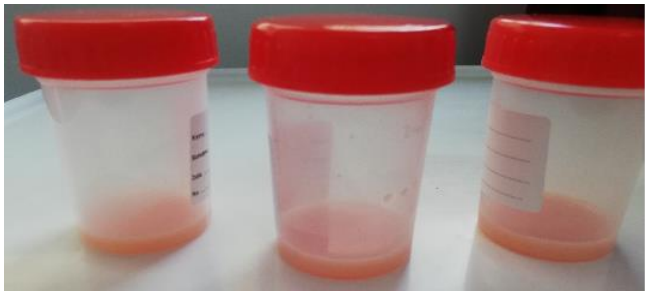

Figure 6: Pleural fluid with a milky macroscopic appearance

Our patient exhibited infiltrations of the microcystic structures affecting the bilateral inguinal regions, along with infiltration of the perineal region and multiple osteolytic lesions involving the sacrum and bilateral iliac wings, accompanied by chylothorax. This presentation encompasses both superficial and deep lymphatic malformations (LCMs) and is a notably rare manifestation of the disease.

Diagnosis LCMs is typically delayed due to the rarity of the pathology, and the varied clinical presentations based on the specific organs affected (1,8).

The disease may occasionally present with such nonspecific symptoms as tracheal wheezing, dry cough, chest pain, dyspnea, tightness and wheezing, often leading to misdiagnosis as asthma or other respiratory pathologies. Significant pleural effusion, frequently chylous in nature, may be associated with chylopericardium and progressive pulmonary infiltration, with the potential to result in respiratory failure (8).

Chest X-rays may reveal interstitial involvement along with pleural effusion, although such findings are not specific to LCMs (1).

CT imaging exposes patients to radiation and falls short of the diagnostic value of magnetic resonance imaging (MRI). Lymphography can assess the extent of lesions, although this technique carries the risk of pulmonary complications – a concern also applicable to isotopic lymphoscintigraphy – and so both methods are of limited utility in the evaluation of LCMs (1,8).

MRI is thus the preferred modality for assessing anatomical extent and for the effective characterization of lesions. Magnetic resonance lymphography employs highly T2-weighted sequences to provide a detailed anatomical representation of structures containing stationary or slow-moving fluids. The primary objectives of magnetic resonance lymphography are to localize the source of the leak, to identify any aneurysmal dilatation of the thoracic duct or its afferent vessels, and to evaluate the permeability of the thoracic duct. The technique can also visualize lymphangiectasias relevant to the peribronchovascular lymphatics, the lymphatics of the interlobular septa and even the extravasation of lymph within the alveoli (10).

There is no specific biological test for LCMs, but biopsy is seldom required as diagnoses are primarily based on clinical and radiological findings (1).

The progression of LCMs is characterized by asymptomatic intervals interspersed with episodes of painful inflammation, superinfection or intracystic hemorrhage, and is particularly accelerated in puberty, although the influence of hormones has not been definitively established (1).

There remains a lack of consensus on the optimum the treatment of LCMs with pleural effusion, given the rarity and relative obscurity of the condition (8).

The initial management of chylothorax typically involves dietary modifications and thoracentesis (2). Various treatments have been explored for the treatment of lymphatic malformations, including glucocorticoids, bisphosphonates, imatinib, thalidomide, interferon, cyclophosphamide, tamoxifen and sildenafil, as well as sclerotherapy and radiotherapy. While these therapies have shown benefits in certain patients, they may also be associated with significant adverse effects (7). Propranolol and bevacizumab have also been tried as treatments for LCM, but there is insufficient evidence to recommend their use (1,7).

Genetically, LCMs have been associated with an activating somatic post-zygotic mutation in the PIK3CA gene that disrupts and activates the PI3K/AKT/mTOR cell signaling pathway involved in lymphangiogenesis. This alteration is been shown to respond well to mTOR inhibitors. mTOR inhibitors have been used to treat complicated LCMs since 2011, and have produced promising results (2,3,8,11,12).

Several authors have reported significant improvements in patients treated with mTOR inhibitors:

In 2016, Nadal et al. (13) reported on 83 cases with vascular anomalies who were managed with mTOR inhibitors, noting the efficacy of 2 weeks to 6 months treatment.

Nasser et al. (6) reported a case of a 32-year-old woman who presented with cardiac tamponade, mediastinal infiltration and pleural effusion, and whose treatment with an mTOR inhibitor resulted in clinical improvement after 10 months, and the resolution of both the mediastinal infiltration and pleural and pericardial effusions.

In a 2011 study by El Zein et al. (3), a 25-year-old patient with a giant unresectable mesenteric cystic lymphangioma associated with a mutation in the PIK3CA gene was treated with an mTOR inhibitor, resulting in a favorable response, allowing a complete resection of the lesions after 9 months of treatment and subsequent cure.

In 2024, Chang et al. (2) published the case of a 12-year-old patient who presented with both superficial and deep LCMs involving the mucocutaneous region and parotid gland. A genetic analysis revealed a somatic PIK3CA mutation, and the patient was subsequently treated with an mTOR inhibitor, resulting in the resolution of the lesions after 4 months.

mTOR inhibitor treatments can lead to significant, although incomplete, improvements in most cases with LCMs, but are reserved primarily for the more complex and severe cases. The treatment period is typically long, and there are currently no established criteria for discontinuation other than the presence of adverse effects (1).

Adverse effects may be clinical, including gastrointestinal disorders, asthenia, headaches, hypersensitivity pneumonitis and venous thrombosis; or biological, such as thrombocytopenia, anemia, lymphopenia and neutropenia. Consequently, regular clinical and biological monitoring is necessary, starting 1 month after the initiation of treatment and every 2 to 3 months thereafter (1)

Targeted therapies, particularly anti-PI3K agents, are currently under clinical evaluation (1).

Surgical interventions are typically reserved for cases with advanced stages of the disease that are resistant to the pharmacological treatments, and typically involve thoracotomy with pleurectomy. More favorable outcomes reported with pleurectomy, either with or without thoracic duct ligation, however, thoracic duct ligation alone is not effective, indicating that the source of lymphatic fluid does not originate solely from the thoracic duct, but rather from aberrant lymphatic vessels within the chest wall. The application of fibrin glue (Tisseel) can support the control of lymphatic leakage and prevent postoperative recurrence (8,9,14).

Patients with LCMs and their caregivers require regular psychological support (1).

CONCLUSION

Lymphatic malformations (LCMs) are a significant and potentially disabling condition. In the present study, mTOR inhibitors were found to be effective in alleviating the patient's symptoms, similar to numerous cases reported in the literature. The duration of treatment is prolonged, and there are currently no established criteria for discontinuation. Other targeted therapies are currently under evaluation, while surgical interventions continue to be reserved for severe cases that are resistant to alternative treatment options.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - M.K.A., L.S., B.A., M.S.; Planning and Design - M.K.A., L.S., B.A., M.S.; Supervision - M.K.A., L.S., B.A., M.S.; Funding - M.K.A., M.S.; Materials - M.K.A., M.S.; Data Collection and/or Processing - M.K.A.; Analysis and/or Interpretation - M.K.A., M.S.; Literature Review -

M.K.A.; Writing - M.K.A.; Critical Review - M.K.A., L.S., B.A., M.S.

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RESPIRATORY CASE REPORTS

Pulmonary Carcinosarcoma: A Case Series of Seven Patients and Review of the Literature

Pulmoner Karsinosarkom: Yedi Hastalık Olgu Serisi ve Literatürün Gözden Geçirilmesi

Rajae Amiali[1], Btissame Es-Sabbahi[1], Lamiyae Senhaji[1], Mariem Karhate Andaloussi[1], Mounia Serraj[1], Elbizae Mohammed[1], Badreeddine Alami[2], Smahi Mohamed[3], Bouchra Amara[1]

Abstract

Pulmonary carcinosarcoma is a rare neoplasm of the lung that accounts for 0.3–1% of all primary lung cancer cases, and is characterized by the presence of both carcinomatous epithelial and malignant mesenchymal components. Tumors exhibit aggressive behavior and significant metastatic potential, and there is a high likelihood of recurrence. The primary treatment is surgical, however, the two-year survival rate remains below 10%. We present here an analysis of seven patients diagnosed with lung carcinosarcoma whose diagnosis was confirmed through histopathological examination and the immunohistochemical analysis of tumor biopsies. This case series provides new insights into the clinical characteristics and treatment outcomes of pulmonary carcinosarcoma, highlighting potential differences in a comparison with existing literature.

Keywords: *Pulmonary, carcinosarcoma, cancer, sarkom.*

Öz

Pulmoner karsinosarkom, akciğerin nadir bir neoplazmıdır ve primer akciğer kanseri olgularının %0,3 ila %1'ini oluşturur. Hem karsinomatöz epitel hem de malign mezenkimal bileşenlerin varlığı ile karakterizedir. Bu tümörler, agresif davranış, önemli metastatik potansiyel ve yüksek nüks olasılığı gösterirler. Tedavi öncelikle cerrahidir; ancak iki yıllık sağkalım oranı %10'un altında kalmaktadır. Bu makalede akciğer karsinosarkomu tanısı alan yedi hastanın analizinden elde edilen bulguları sunuyoruz. Tanı, tümör biyopsilerinin histopatolojik incelemesi ve immünohistokimyasal analizi ile doğrulandı. Bu olgu serisi, pulmoner karsinosarkomun klinik özelliklerine ve tedavi sonuçlarına yeni bilgiler ekleyerek, mevcut literatür ile karşılaştırıldığında potansiyel farklılıkları vurgulamaktadır.

Anahtar Kelimeler: *Pulmoner, karsinosarkom, kanser, sarkom.*

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Sarcomatoid carcinoma of the lung (SCC) is an uncommon primary non-small-cell lung cancer variant, five subtypes of which have been identified by the World Health Organization (WHO): carcinosarcomas, giant cell carcinomas, pleomorphic carcinomas, spindle cell carcinomas and pulmonary blastomas (1,2). Carcinosarcoma is a specific subtype of pulmonary sarcomatoid carcinomas that is characterized by high aggressiveness, significant metastatic potential and an elevated risk of recurrence. Diagnosis is established based on histopathological and immunohistochemical findings (3).

Surgery with complete resection is the primary treatment for non-metastatic disease. In contrast, chemotherapy or radiotherapy is preferred for the management of advanced pulmonary carcinosarcoma (2). In the present study we evaluate the treatment responses and prognostic factors of our patient cohort over a two-year period, from January 2022 to January 2024, and compare our findings with existing literature.

CASE

Case 1: A 53-year-old passive smoker presented with left-sided pleuritic chest pain and low-volume hemoptysis of 50 ml per day. The patient's WHO performance status was 0, and oxygen saturation was 97% in ambient air. A comprehensive pleuropulmonary examination revealed normal findings.

Chest computed tomography (CT) identified a small left pleural effusion, and the patient was staged as non-metastatic, with an 80 mm long-axis lesion in the left lower lobe, and as PT4N0 due to the size and extent of the lesion. A fibroscopy biopsy was attempted but was inconclusive. Given the high probability of malignancy and the absence of distant metastases, the decision was made to proceed with a left lower lobectomy and radical mediastinal lymph node dissection. A histopathological evaluation, supplemented by an immunohistochemical (IHC) analysis, confirmed the diagnosis of pulmonary carcinosarcoma. Following surgery, the patient received adjuvant chemotherapy that resulted in favorable outcomes.

Case 2: A 66-year-old chronic smoker with a 40-year smoking history presented with low-volume hemoptysis of less than 50 ml per day and notable weight loss of 6 kg. The patient's WHO performance status was 0, and oxygen saturation (SpO_2) was 96% in ambient air. A comprehensive pleuropulmonary examination revealed normal findings, while chest CT revealed a suspicious 3 cm mass in the left upper lobe. A subsequent positron emission tomography (PET) scan identified a hypermetabolic nodule in the left upper lobe measuring 30*29 mm, with no suspicious active foci detected in the remaining explored areas (Figure 1).

An attempted fibroscopy failed to reach the lesion, and the biopsy results were inconclusive due to a high probability of malignancy. Given the absence of distant metastases, the decision was made to proceed with a left upper lobectomy and radical mediastinal lymph node dissection. The histopathological examination and additional IHC analysis confirmed the diagnosis of pulmonary carcinosarcoma, and the patient was started subsequently on adjuvant chemotherapy, with favorable outcomes.

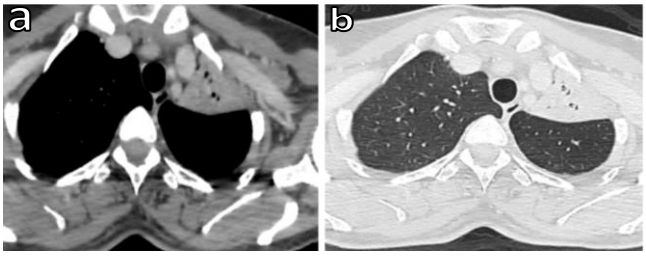

Figure 1: *Thoracic CT scan in mediastinal and parenchymal windows showing a left upper lobar tumor mass*

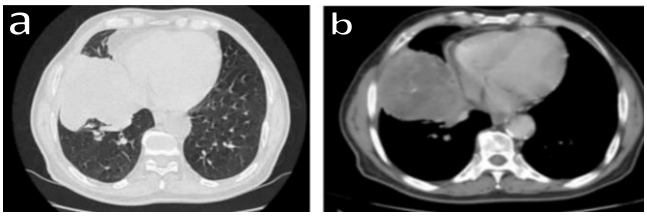

Figure 2: *Thoracic CT scan in parenchymal* ***(a)*** *and mediastinal* ***(b)*** *windows showing a middle lobar tumour mass with regular thickening of the pleural sheets opposite*

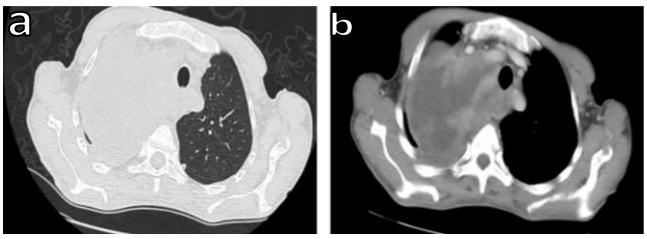

Figure 3: *Thoracic CT scan in the parenchymal window* ***(a)*** *and mediastinal window* ***(b)*** *revealed a right mediastinal-pulmonary tumor mass measuring 120 x 66 mm, in close contact with the trachea, esophagus, and thyroid*

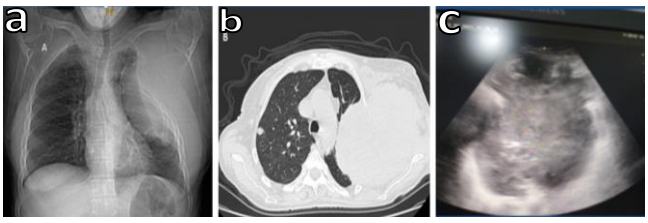

Figure 4: ***(a)*** *Frontal chest X-ray revealed a water-toned opacity occupying the upper two-thirds of the left lung field, with outer margins merging with the chest wall and extending beyond the limits of the thorax, accompanied by costal lysis on the opposite side.* ***(b)*** *Chest CT scan in the parenchymal window displayed a tumoral mass in the left hemithorax, characterized by soft tissue invasion and costal lysis on the opposite side, along with a nodule in the contralateral lung.* ***(c)*** *Ultrasound examination showed a roughly rounded tumor with irregular contours and a heterogeneous echostructure.*

Table 1: Summary Table of Pulmonary Carcinosarcoma Cases

Case Number	Patient Age (years)	Patient Sex	Smoking History	Initial Symptoms	Clinical Findings	Imaging Results	Staging	Diagnosis	Treatment	Surgical Details	Outcome
Case 1	53	Male	Yes	Left-sided pleuritic chest pain, hemoptysis (50 ml/day)	WHO performance status 0, oxygen saturation 97%	Small left pleural effusion; 80 mm lesion	PT4N0	Pulmonary carcinosarcoma	Left lower lobectomy; adjuvant chemotherapy	Radical mediastinal lymph node dissection	Favorable outcomes
Case 2	66	Male	Yes	Hemoptysis (<50 ml/day), weight loss (6 kg)	WHO performance status 0, oxygen saturation 96%	Suspicious 3 cm mass in left upper lobe	PT2N0	Pulmonary carcinosarcoma	Left upper lobectomy; adjuvant chemotherapy	Radical mediastinal lymph node dissection	Favorable outcomes
Case 3	68	Male	Yes	Unexplained weight loss	Mid-lobar mass, lymphadenopathy	CT showed mass with pleural thickening	IVB	Pulmonary carcinosarcoma	Referred for chemotherapy; advanced stage		Passed away prior to treatment
Case 4	63	Male	Yes	Chest pain, dysphonia, dysphagia	WHO performance status 2, oxygen saturation 87%	Right mediastinal-pulmonary tumor mass	IVB	Pulmonary carcinosarcoma	Referred for chemotherapy; advanced stage		Passed away prior to treatment
Case 5	63	Female	No	Chest pain, dyspnea on exertion	WHO performance status 3, large left chest mass	Large heterogeneous mass, rib osteolysis	IVB	Pulmonary carcinosarcoma	Ultrasound-guided biopsy; advanced stage; chemotherapy planned		Passed away prior to treatment
Case 6	61	Male	Yes	Right-sided chest pain	WHO performance status 2, oxygen saturation 96%	Tissue mass in right upper lobe	IVB	Pulmonary carcinosarcoma	Biopsy confirmed diagnosis; planned for chemotherapy		Lost to follow-up
Case 7	58	Male	Yes	Abdominal pain, vomiting, weight loss	Normal clinical examination; pulmonary nodules identified	CT confirmed adrenal incidentaloma	IVB	Pulmonary carcinosarcoma	Initiated on chemotherapy; advanced stage		Succumbed to disease

Case 3: A 68-year-old chronic smoker with a 40-year history of smoking presented without respiratory symptoms. To find the reason for the unexplained weight loss, a chest computed tomography (CT) scan was conducted revealing a mid-lobar mass with regular thickening of the adjacent pleural layers and lymphadenopathy in the Baretey compartment (Figure 2).

Bronchoscopy identified a tumor bud that was obstructing two-thirds of the trachea. A histopathological examination, complemented by additional immunohistochemical (IHC) analysis, confirmed the diagnosis of pulmonary carcinosarcoma. An extension assessment indicated no evidence of distant metastases, and the patient was subsequently referred for chemotherapy. Having been diagnosed at an advanced IVB stage, the patient expired prior to the initiation of treatment, with the cause of death attributed to the advanced stage of the disease.

Case 4: A 63-year-old chronic smoker with a 10-year smoking history presented with chest pain, dysphonia and dysphagia, unexplained weight loss. The patient's WHO performance status was 2 < 50% in bed during the day, with oxygen saturation at 87% in ambient air and signs of central venous congestion. Thoracic CT revealed a right mediastinal-pulmonary tumor mass measuring 120 x 66 mm that was in contact with the trachea and esophagus. There was minimal bilateral pleural effusion, along with secondary pulmonary nodules and metastatic lesions in the axial skeleton (Figure 3). Bronchoscopy revealed complete invasive and budding stenosis of the middle lobe, and a histopathological analysis confirmed pulmonary carcinosarcoma. The patient was referred for chemotherapy, but given his advanced IVB stage he succumbed to the disease prior to the initiation of treatment, with the cause of death linked to the advanced stage of the disease.

Case 5: A 63-year-old female non-smoker with a 10-year history of diabetes presented with chest pain and dyspnea on exertion, coinciding with a deterioration in her overall condition. The patient's WHO performance status was assessed as 3, and a large left-sided chest mass measuring over 7 cm was identified. Computed tomography (CT) revealed a large heterogeneous mass in the lateral aspect of the left hemithorax that extended into the axillary region, with evidence of osteolysis affecting the first four ribs (Figure 4). An ultrasound-guided biopsy confirmed the diagnosis of pulmonary carcinosarcoma, while an extension assessment indicated the presence of metastases in the brain and liver. The patient was subsequently referred for chemotherapy; but expired prior to the initiation of treatment, with the cause of death attributed to the advanced stage of the disease.

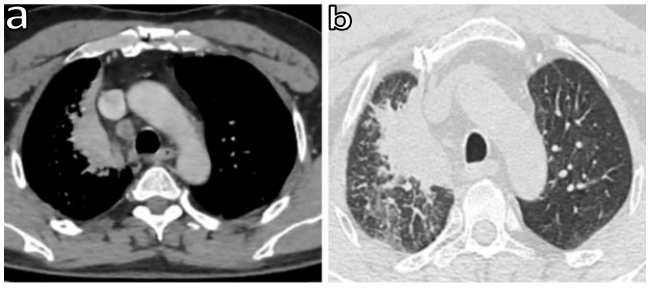

Figure 5: *Thoracic computed tomography (CT) in mediastinal and parenchymal windows reveals a tumor process affecting the ventral segment of the upper right lobe, measuring 8 cm in size. The mass exhibits irregular contours, indicating an aggressive process*

Case 5: A 63-year-old female non-smoker with a 10-year history of diabetes presented with chest pain and dyspnea on exertion, coinciding with a deterioration in her overall condition. The patient's WHO performance status was assessed as 3, and a large left-sided chest mass measuring over 7 cm was identified. Computed tomography (CT) revealed a large heterogeneous mass in the lateral aspect of the left hemithorax that extended into the axillary region, with evidence of osteolysis affecting the first four ribs (Figure 4). An ultrasound-guided biopsy confirmed the diagnosis of pulmonary carcinosarcoma, while an extension assessment indicated the presence of metastases in the brain and liver. The patient was subsequently referred for chemotherapy; but expired prior to the initiation of treatment, with the cause of death attributed to the advanced stage of the disease.

DISCUSSION

Pulmonary carcinosarcoma is a rare form of tumor. A retrospective cohort study conducted in the United States (SEER: Surveillance, Epidemiology, and End Results) involving 1,052,108 patients diagnosed with malignant tumors of the lung or bronchus reported a prevalence of 0.05% – which is notably lower than the 1% prevalence reported in the present study and may be attributed to differences in sample size (4).

The World Health Organization (WHO) revised the classification criteria for lung cancers in 2004, recommending "sarcomatoid carcinoma" be used as the umbrella term for the range of non-small cell lung cancers with sarcomatous components or that exhibit sarcomatous differentiation (5).

Pulmonary carcinosarcoma is more prevalent in older men in the United States (2), which is consistent with the male/female ratio of 2.5 and a mean age of 61.7±5.25 years identified in the present study.

Clinical signs of pulmonary carcinosarcoma are nonspecific, and depend on the tumor's location. The central endobronchial form typically presents with such symptoms as cough, hemoptysis, dyspnea and recurrent pneumonitis. Conversely, the peripheral form, which is associated

with a poorer prognosis, may present with pain due to the invasion of the chest wall. Additionally, incidental radiological findings have been reported in 6.7% of cases (6). Such tumors predominantly present as peripheral lung masses on CT scans, and are sometimes excavated, invading the pleura and chest wall, or proximal endobronchial or diffuse tumor masses (7). One case in our series had the central form, while the remaining patients exhibited peripheral involvement.

Patients with lung carcinosarcoma do not appear to respond more favorably to standard treatments or to have a better prognosis than those with other types of lung cancer. Complete resection remains the primary treatment for non-metastatic forms of the disease, while for advanced-stage carcinosarcoma, chemotherapy or radiotherapy are often preferred over surgical resection, contributing to intrinsically poor survival outcomes.

Stereotactic body radiation therapy (SBRT) has emerged as an effective treatment modality for inoperable lung carcinosarcoma, with one study even claiming superior survival benefits to conventional fractionated radiotherapy (8). In addition to radiotherapy, chemotherapy has demonstrated some therapeutic efficacy (9).

Targeted treatments with pazopanib have also demonstrated favorable responses in cases of metastatic carcinosarcoma (10). The prognosis for this type of cancer remains poor, with a two-year survival rate of less than 10%, with poorer prognoses associated with tumor size, the presence of distant metastases and the size of the sarcomatous component. Of the seven cases presented here, four succumbed to their illness.

CONCLUSION

Given the rarity of carcinosarcoma, which typically present in adevnced stages, the overall prognosis remains dismal despite advances in treatment modalities. Although the benefits of many of these modalities have yet to be evaluated in large-scale prospective randomized trials, the rarity of the disease suggests such studies are unlikely.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - R.A., B.E.S, L.S., M.K.A., M.S., E.M., B.A., S.M., B. A.; Planning and Design - R.A., B.E.S, L.S., M.K.A., M.S., E.M., B.A., S.M., B. A.; Supervision - R.A., B.E.S, L.S., M.K.A., M.S., E.M., B.A., S.M., B. A.; Funding - R.A., B. A.; Materials - R.A., B. A.; Data Collection and/or Processing - R.A.; Analysis and/or Interpretation - R.A., B. A.; Literature Review - R.A..; Writing - R.A.; Critical Review - R.A., B.E.S, L.S., M.K.A., M.S., E.M., B.A., S.M., B. A.

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Respir Case Rep 2025;14(1): 12-14 DOI: 10.5505/respircase.2025.33602

RESPIRATORY CASE REPORTS

Pulmonary Actinomycosis: A Case Report

Pulmoner Aktinomikoz: Olgu Sunumu

Hande Karadeniz[1], İbrahim Güven Çoşğun[2], Sena Naz Adsız Dayanç[3]

Abstract

Pulmonary actinomycosis is a bacterial disease caused by actinomyces species with nonspecific clinical and radiologic findings that make it difficult to diagnose, and that is mistaken for malignancy. We present here the case of 29-year-old woman who was admitted to our hospital with a cough that had been intermittently worsening for the last 3 years, and who was diagnosed with pulmonary actinomycosis based on transbronchial biopsy, despite the absence of bronchoscopic lesions.

Keywords: *Actinomycosis, endobronchial, bronchoscopy.*

Öz

Pulmoner aktinomikozis, aktinomiçes türlerinin neden olduğu, nonspesifik klinik ve radyolojik bulguları olması nedeni ile doğru tanı konulmasında güçlük yaşanan, çoğunlukla malignite olarak değerlendirilen bakteriyel bir hastalıktır. Yirmi dokuz yaşında kadın hasta, son üç yıldır aralıklı olarak alevlenen öksürük şikâyeti ile başvurdu. Burada, bronkoskopik lezyon izlenmemesine rağmen transbronşial biyopsi incelemesinde pulmoner aktinomiçes tanısı alan olgumuz nadir görülmesi nedeniyle sunuldu.

Anahtar Kelimeler: *Aktinomikoz, endobronşiyal, bronkoskopi.*

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Actinomycosis is a chronic and rare infection associated with gram-positive, immobile anaerobic bacteria, usually involving the cervicofacial region, and more rarely the thorax, and abdominal, cerebral and laryngeal regions (1,2). It is a subacute or chronic infection that often mimics malignant lesions (2). Nodules, which may be confused with lung cancer on PA chest radiography, may present with consolidation or mass formation (3). Pulmonary actinomycosis accounts for 15% of all actinomycosis cases, and an accurate and timely diagnosis is made in only 4–7% of cases (4). We present here the case of a 29-year-old patient with pulmonary actinomycosis diagnosis who was treated for similar complaints 5 years earlier with a history of dental procedures.

CASE

A 29-year-old woman was admitted to our clinic with a complaint of chronic cough, but no additional complaints such as chest pain, dyspnea or night sweats. The patient had undergone thyroidectomy for a toxic multinodular goiter and had been receiving levothyronine treatment. Here history included a monodermal teratoma that had been detected on the left ovary and surgically removed 1 year earlier, and admission to a medical center with cough and nausea 5 years ago when computed tomography of the right lower lobe superior segment revealed a bronchiectatic area. The patient had no smoking or alcohol history, and a history of dental prosthesis procedures. On physical examination, the patient was 158 cm, 49 kg, BMI 19.6, in good general condition, oriented and cooperative, while rales in the lower zones of the right lung were identified on respiration. Chest radiography and pulmonary computed tomography showed an area of increased density in soft tissues measuring 30.5 x 22 mm in the superior segment of the right lung lower lobe, and distal areas of trapped air (Figures 1 and 2). Bronchoscopy revealed no endobronchial lesions. The bronchial lavage was removed and a transbronchial biopsy was performed, and a pathologic examination of the transbronchial biopsy specimens revealed inflamed bronchial mucosa and cotton-like microorganism structures intertwined with bronchial epithelium. The samples were stained black for a methanamine sulfide histochemical study revealing branching hyphae structures (Figure 3). ARB was negative in the microbial examination. The patient was diagnosed with pulmonary actinomycosis, and was hospitalized and treated with intravenous sulbactam-ampicillin 4 x 1g. Partial regression of the infiltration in the right middle zone was observed in a control chest radiograph taken in the 3rd month of treatment (Figure 4). Her treatment is continuing.

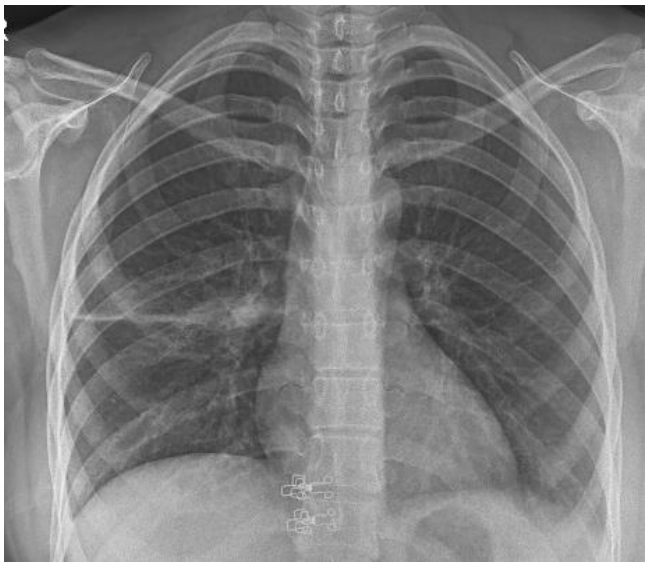

Figure 1: Chest X-ray displaying consolation in the right-middle zone

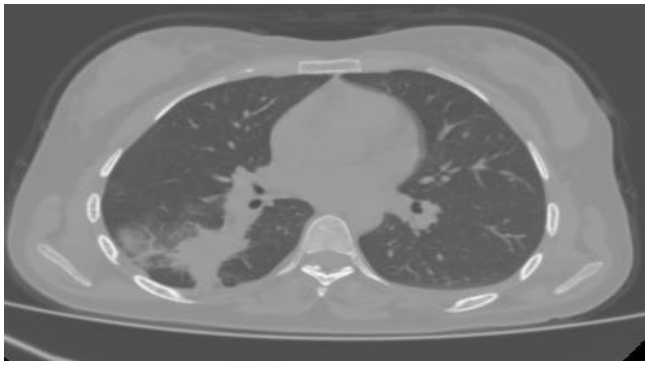

Figure 2: Chest computed tomography showed an area of parenchymal consolidation in the superior segment of the upper right lower of the lung

DISCUSSION

Pulmonary actinomycosis continues to be diagnostically challenging for physicians due to the difficulties in differentiating from other diseases of the lung. Patients may present with nonspecific symptoms such as fever, cough, sputum, night sweats and weight loss (5). Immunosuppressive diseases such as chronic bronchitis, emphysema, poor oral hygiene, periodontal surgery, cervicofacial trauma and diabetes mellitus have been identified as predisposing factors for actinomycosis (6). Our patient presented with a chronic cough but no accompanying sputum, having presented with similar complaints 3 years earlier when she had received partial treatment. Her history included a periodontal intervention and poor oral hygiene, and an 18F-FDG PET/CT performed during the follow-up of an ovarian monodermal teratoma revealed FDG uptake in the left ovarian lobe and Dougles cavity and in the posterior segments of the upper lobe of the right lung. Bronchoscopy was planned to investigate the etiology of the chronic cough and pathologic uptake on imaging. Pathological examinations of biopsy specimens and the production of microorganisms in culture contribute diagnoses of actinomycosis (7). Bronchoscopy may

reveal exophytic masses characterized by purulent exudate and sulfur granules (5). In the presented case, the diagnosis was made with the demonstration of branching hyphae-like structures stained black with methenamine-silver belonging to actinomycosis on pathological examination of the biopsy specimen obtained after bronchoscopy. Beta-lactam antibiotics are among the preferred treatments, the duration of which can extend to 6–8 months (8). Patients with penicillin allergies may benefit from such alternatives as tetracycline, erythromycin and chloramphenicol (9). Surgery may be advised in the event of such complications as pulmonary abscesses and empyema, as well as the drainage of fistulas and sinuses (10). The patient in the present study was started on intravenous ampicillin-sulbactam 4x1gr iv treatment, which was switched to 2x1gr orally during follow-up. The patient's treatment is continuing.

CONCLUSION

Pulmonary actinomycosis continues to be clinically challenging for physicians. Bronchoscopy is a key diagnostic tool in patients with prolonged symptoms that fail to resolve under empirical antibiotic therapy. We present this case to emphasize that pulmonary actinomycosis should be considered in the differential diagnosis of cases with late-responding or recurrent pneumonia.

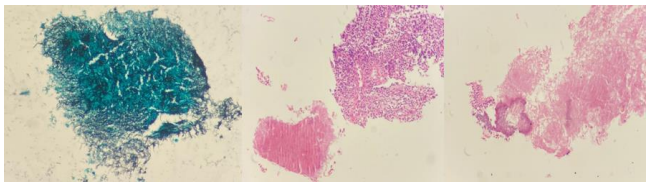

Figure 3: *Branching hyphae-like actinomyces microorganism structures stained black for a methenamine-silver histochemical study (X400)*

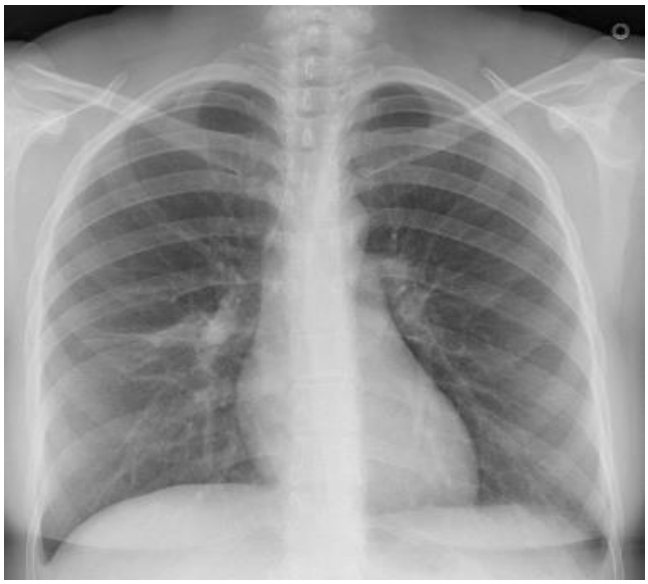

Figure 4: *Partial regression of the infiltration in the right middle zone observed on chest radiograph taken at the 3rd month of treatment*

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - H.K., İ.G.Ç., S.N.A.D.; Planning and Design - H.K., İ.G.Ç., S.N.A.D.; Supervision - H.K., İ.G.Ç., S.N.A.D.; Funding -; Materials - H.K., İ.G.Ç., S.N.A.D.; Data Collection and/or Processing - H.K., İ.G.Ç., S.N.A.D.; Analysis and/or Interpretation - H.K., İ.G.Ç., S.N.A.D.; Literature Review - H.K., İ.G.Ç.; Writing - H.K., İ.G.Ç.; Critical Review - H.K., İ.G.Ç.

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A Rare Causative Agent in Hospital-acquired Pneumonia: *Hafnia Alvei*

Hastane Kaynaklı Pnömonide Nadir Görülen Bir Etken: Hafnia Alvei

Sibel Doruk, Özgür Batum

Abstract

A 67-year-old male with lung cancer presented to the emergency department with complaints of dyspnea, fatigue, cough and sputum, and was admitted to the intensive care unit with a diagnosis of community-acquired pneumonia. Computed thoracic tomography revealed a cavitary consolidation lesion in the left lower lobe, and high C-reactive protein (CRP) and procalcitonin (PCT) were detected. The patient was subsequently transferred to the clinic, where a foul-smelling purulent sputum developed and CRP and PCT were increased. *H. alvei* was isolated form a sputum sample that was resistant to amoxicillin-clavulanate and susceptible to cephalosporins, ciprofloxacin, levofloxacin, carbapenems and piperacillin-tazobactam. The patient was treated with combined empirical antibiotics and then discharged.

Keywords: *H alvei, nasocomial pneumonia, respiratory infections.*

Öz

Nefes darlığı, halsizlik, öksürük ve balgam şikayeti ile acil servise başvuran 67 yaşında akciğer kanserli erkek hasta, yoğun bakım ünitesine toplum kökenli pnömoni tanısı ile yatırıldı. Bilgisayarlı toraks tomografisinde sol alt lobda kaviter konsolidasyon alanı görüldü, yüksek C-reaktif protein (CRP) ve prokalsitonin (PCT) tespit edildi. Sonrasında servise transfer edilen hastada kötü kokulu pürülan balgam gelişti ve CRP ve PCT' de artış tespit edildi, balgam örneğinde amoksisilin-klavulanata dirençli, sefalosporin, siprofloksasin, levofloksasin, karbapanem ve piperasilin-tazobaktam duyarlı *H. alvei* izole edildi ve kombine 14 günlük geniş etkili ampirik antibiyotik ile tedavi edildi.

Anahtar Kelimeler: *H alvei, hastanede gelişen pnömoni, solunum enfeksiyonları.*

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Hafnia alvei is a rod-shaped, gram-negative facultative anaerobic bacillus (1). *H. alvei* was first described by Dr. Bahr as an enterobacteria in 1919 (2), although the taxonomy of the species was not defined until 2010 (3). Although it was thought to be enteropathogenic in the 1990s, it was later determined to be the potential cause of infections in many systems (4,5).

We present here the case of a 67-year-old male with a history of COPD and lung cancer who was admitted to hospital with nosocomial pneumonia caused by *H. alvei*.

CASE

A 67-year-old male patient applied to the emergency service with dyspnea, weakness, cough and sputum was hospitalized in the intensive care unit. The patient had a 50 pack/year smoking history, squamous cell lung cancer diagnosed two years ago that was followed up without treatment over 6 months, and COPD.

A physical examination revealed a respiratory rate of 30 breaths per minute, a pulse of 120 bpm and oxygen saturation of 80% in room air. High levels of C-reactive protein (CRP) (161.8 mg/L) and procalcitonin (PCT) (0.17 microgram/L) were detected, while his leukocyte count (WBC) was normal.

A computed thorax tomography (CT) taken in the emergency room was compared with a CT scan taken 8 months earlier following the completion of cancer treatment. The first image revealed a cavity in the left lower lobe and atelectasis (Figure 1), while the CT scan in the emergency room revealed widespread bilateral emphysematous changes, a minimal pleural effusion in the left hemithorax, and an enlargement of the cavity and an area of homogeneous consolidation around the cavity (Figure 2). Intravenous (IV) cefepime initiated. In the qualified sputum specimen (more than 25 polymorphonuclear leukocytes and less than 10 epithelia in each field) on the first day upper respiratory tract flora bacteria grew. The patient was admitted to the Chest Diseases Service on the ninth day of hospitalization after a general improvement was noted in his condition.

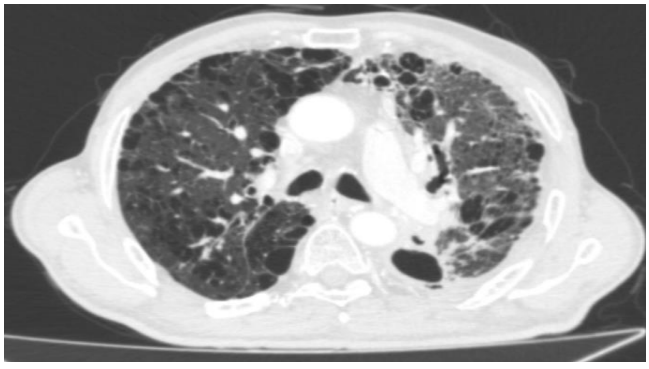

Figure 1: *CT upon the completion of the cancer treatment showing the cavity in the left lower lobe and atelectasis*

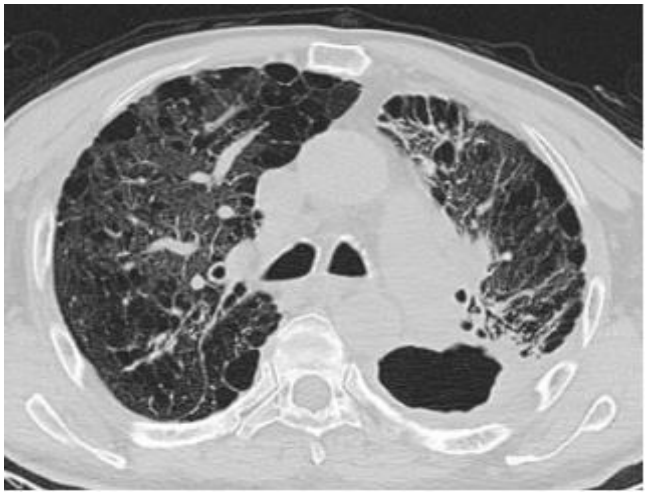

Figure 2: *Emergency room CT revealing the cavitary consolidation in the left lower lobe*

Foul-smelling purulent sputum developed during follow-up, and an increase was detected in acute phase reactants (CRP 234.6 mg/L, WBC 13.8 and PCT 0.2 microgram/L), and so empirical IV meropenem and amikacin initiated. The *H. alvei* isolated from the qualified sputum specimen examined before the empirical antibiotic change was resistant to amoxicillin-clavulanate and susceptible to cefepime, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, levofloxacin, imipenem, meropenem and piperacillin-tazobactam. Following an antibiotic susceptibility test performed to EURCAST 2023 standards, the patient was started on a 14-day program of combined empirical antibiotics and then discharged.

DISCUSSION

H. alvei, known more formerly as *Enterobacter hafniae* or "*paracolon*" bacterium, is a member of the Enterobacteriaceae family and is a facultative anaerobic gram-negative bacillus. It is rarely considered pathogenic in immunocompetent patients, and it is generally referred to as oropharyngeal and enteric commensal (6). *H. alvei* can thrive in several different environments, such as fish farms, rivers, polluted waters and sewage (7,8). The bacterium can also be found in the digestive tracts of many animals (9). Some *H. alvei* strains have developed as opportunistic pathogens in several animal species, including fish, birds, mammals and insects (10), and have been linked to several diseases in humans (4,7).

H. alvei was considered enteropathogenic in 1991, but has since come to be known to cause wound infections, septicemia, meningitis, urinary tract infections and pneumonia (5). The most frequently reported *H. alvei* infections are those of the urinary tract, followed by intra-abdominal, bloodstream, respiratory tract, and bone or soft tissue infections (4). Most reported cases are hospital-acquired although the origin of the infections has not

been well established (2). *H. alvei* is rarely identified in community-acquired pneumonia in immunocompetent adults (11).

H. alvei can cause serious infections in adults, especially those hospitalized with chronic diseases, subjected to invasive procedures or under antibiotic therapy (12,13). The presented case had COPD and lung cancer, and was treated with broad-spectrum antibiotics upon hospitalization.

Klapholz et al. (6) reported seven cases with H.alvei-positive sputum cultures in a hospital over a 3-year period, all of whom had comorbidities, but only one had a pure growth of *H alvei* confirmed by a culture obtained from a bronchoscopic protected brush specimen. All of the *H. alvei* isolates identified in were resistant to conventional antibiotics, including penicillin and cephalosporins (6). Our patient resembled these reported cases in many aspects, including his serious comorbidity and the *H alvei* isolated from his sputum culture.

H. alvei is resistant to penicillin, amoxicillin/clavulanate and macrolides (6), and as a result of this resistance to so many first-line antibiotics, *H. alvei* pneumonia is generally treated with carbapenems or cephalosporins. In the case reported by Lim et al. (11), *H. alvei* was resistant to amoxicillin/clavulanate, and sensitive to ceftriaxone, cefotaxime, piperacillin/tazobactam, levofloxacin, ciprofloxacin, gentamicin, meropenem and imipenem, leading them to treat their patient with empiric amoxicillin/clavulanate and clarithromycin. Our case had similar antibiogram findings from the sputum culture. ERS/ESICM/ESCMID/ALAT HAP and VAP guideline, in patients without XDR and PDR, it is recommended to treat with a single drug according to antibiotic susceptibility (14). The long-term hospitalization of our patient, the previous broad-spectrum antibiotic therapy and the presence of a cavity supported the decision to start the patient on combined antibiotic therapy.

H. alvei is rare in cases of hospital-acquired pneumonia, and its sensitivity to empirical broad-spectrum antibiotics, as the generally preferred treatment. This sensitivity leads to its good prognosis. A culture examination revealed our patient to be sensitive to such a treatment, leading us to opt for a 14-day combined empirical antibiotic approach, and the patient was duly discharged.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - S.D., Ö.B.; Planning and Design - S.D., Ö.B.; Supervision - S.D., Ö.B.; Funding - S.D., Ö.B.; Materials - S.D.; Data Collection and/or Processing -; Analysis and/or Interpretation -; Literature Review - S.D.; Writing - S.D.; Critical Review - S.D.

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A Rare Cause of Recurrent Pneumonia: Common Variable Immunodeficiency

Sık Tekrarlayan Pnömonilerin Nadir Bir Nedeni: Yaygın Değişken İmmün Yetmezlik

Zeynep Çetinkaya, Coşkun Doğan

Abstract

Common Variable Immunodeficiency (CVID) is a rare underlying cause of frequent recurrent pneumonia in adults. The primary pathophysiology of CVID is impaired antibody response to the antigens associated with immunoglobulin deficiency, resulting from B lymphocyte pathologies. Frequent recurrent upper and lower respiratory tract infections, accompanying autoimmune comorbidities, and significant associations with malignancies make the early diagnosis and treatment of the condition crucial. We present here the case of a 68-year-old patient diagnosed with CVID following etiological investigations for recurrent pneumonia, discussed in the context of the current literature.

Keywords: *Immunoglobulin, Recurrent Pneumonia, Common Variable Immundeficiency.*

Öz

Erişkin yaş gruplarında sık tekrarlayan pnömonilerin altta yatan nadir bir nedeni de Yaygın Değişken İmmün Yetersizlik hastalığıdır. B lenfosit hücrelerin patolojisi sonucu meydana gelen immuünoglobulin yetersizliği sonucu antijenlere karşı antikor yanıtının bozulması temel fizyopatolojiyi oluşturur. Sık tekrarlayan alt ve üst solunum yolları enfeksiyonları, eşlik eden otoimmün ek hastalıklar ve azımsanmayacak oranda eşlik eden malignitlerden dolayı erken tanı ve tedavi elzemdir. Bu yazıda 68 yaşında sık tekrarlayan pnömoiler nedeni ile etyolojik araştırmalar neticesinde Yaygın Değişken İmmün Yetersizlik hastalığı tanısı alan bir olgu güncel literatür eşliğinde sunulmuştur.

Anahtar Kelimeler: *İmmünglobulin, Tekrarlayan Pnömoni, Yaygın Değişken İmmün Yetersizlik.*

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Common Variable Immunodeficiency (CVID) is the most common primary immunodeficiency (PID) in adults, characterized by impaired immunoglobulin (Ig) production due to defects in B lymphocyte differentiation. This results in defective antibody responses to antigens and an increased susceptibility to infections (1).

The most common clinical presentation of CVID is a recurrent bacterial infection, although it can also develop under various other heterogeneous clinical scenarios, including chronic lung disease, gastrointestinal disorders, increased autoimmune conditions, lymphoproliferative and granulomatous diseases, and, albeit rarely, in cases with an elevated risk of malignancy (2).

The pathophysiology of CVID remains unclear. In contrast to many other primary immunodeficiencies, over 90% of documented CVID cases lack a definitive molecular genetic diagnosis or other causal explanation. Only 10–20% of cases have a positive family history, as the majority occurs sporadically (3).

CVID diagnoses are based on reduced serum IgG levels accompanied by decreased IgM or IgA levels and poor vaccine response, after all other causes of hypogammaglobulinemia have been excluded. The cornerstone treatment includes antibiotics for infections and immunoglobulin replacement therapy (4).

We present here the case of a 68-year-old female patient diagnosed with CVID – a condition that is typically identified in childhood or early adulthood – aiming to highlight the need to consider CVID when making advanced evaluations of recurrent pneumonia, especially in older patients.

CASE

A 68-year-old female patient presented to the Pulmonology outpatient clinic with complaints of chills, shivering, coughing and stabbing chest pain during inspiration. Her medical history revealed a diagnosis of chronic lymphocytic leukemia (CLL) 10 years ago and a COVID-19 infection 2 years earlier. Her family history included a cousin with CLL. The patient had a 1-pack/year smoking history and no history of tuberculosis exposure.

On physical examination, the patient's vital signs were stable, while rales were identified in the right upper lung zone on auscultation. Additionally, a 1.5 cm lymphadenopathy was identified in both the right and left inguinal regions on palpitation. A posterior-anterior chest X-ray revealed an increased density in the right upper lung zone (Figure 1), while a thoracic computed tomography (CT) revealed an area of consolidation containing air bronchograms in the posterior segment of the right upper lobe. Also noted in the report were "several mediastinal lymph nodes, the largest measuring 1 cm in diameter, and bilateral axillary lymph nodes with the largest measuring 11 mm in diameter with prominent cortical thickening" (Figure 2). Laboratory tests revealed elevated acute-phase reactants, lymphocyte-predominant leukocytosis and increased C-reactive protein (CRP) levels (Table 1).

The patient was admitted to our department for follow-up and treatment with a preliminary diagnosis of pneumonia. Given her history of antibiotic use 1 month prior, antibiotic therapy of piperacillin-tazobactam (4x4.5 grams) and ciprofloxacin (2x500 milligrams) was initiated.

Table 1: Laboratory Values of the Case

Sr. No.	Foods items	Common points
WBC (103Ul)	46.2	4.00-10.00
CRP (µg/L)	250	0-5
Procalsitonin (mg/dL)	1.06	<0,5
Urea (g/dL)	45	16.6-48.5
Creatinin (mg/dL)	1.03	0.7-1.2
IgG (g/L)	5.9 / 6.5 (c)	7.0-16.0
IgA (g/L)	0.7 / 0.68 (c)	0.7-4,0
IgM (g/L)	0.22 / 0.3 (c)	0.4-2.3
IgG-1 (g/L)	5.19	4.05-10.11
IgG-2 (g/L)	0.55	1.69-7.86
IgG-3 (g/L)	0.108	0.11-0.85
IgG-4 (g/L)	0.046	0.03-2.01
CMV PCR (Iu/mL)	Negative	20-190000
EBV DNA IgG (U/mL)	Undetected	Negative
EBV DNA IgM(U/mL)	Undetected	Negative
Sedimentation mm/saat	22	0-15

c: Control, CRP: C-Reaktif Protein, EBV: Ebstein Bar Virus, mm: Milimetre, Ig:Immunoglobulin, WBC: Leucocyte, LDH: Lactat Dehidrogenase

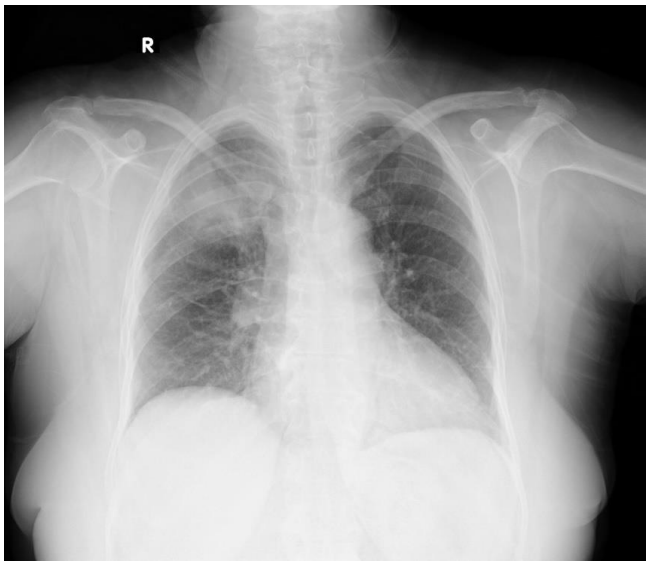

Figure 1: Non-homogenous density increase observed in the right upper zone on PA chest X-ray at the time of hospital admission

A deeper investigation of her medical history revealed frequent upper and lower respiratory tract infections in childhood, tonsillectomy and a history of recurrent pneumonia that had led to multiple hospital admissions. A review of the patient's previous radiological lung images and thoracic CT scans taken 6 and 12 months earlier revealed areas of pneumonic consolidation in different locations (Figures 3 and 4).

In the patient with a history of frequent pneumonia, immunoglobulin (Ig) A, M and G levels and vaccine responses were requested with a preliminary diagnosis of CVID, revealing IgG, A and M levels, as well as control values measured 1 week later, to be low (Table 1). An immunology consultation was requested, and after further investigations, the diagnosis of CVID was confirmed. Intravenous immunoglobulin (IVIG) therapy was initiated upon the recommendation of immunology. The patient was subsequently discharged with follow-up instructions for Pulmonology and Immunology outpatient clinics.

DISCUSSION

This case report relates to a patient diagnosed with Common Variable Immunodeficiency (CVID), a condition most commonly diagnosed in childhood that is relatively rare in adults. If not considered in clinical practice of pulmonology, a diagnosis of CVID may be overlooked. As evidenced by our case and a review of the literature, CVID should be suspected even in older adults with a history of recurrent pneumonia, radiological findings of pneumonic consolidations in different locations and associated malignancies, and in those with lymphoproliferative or autoimmune diseases.

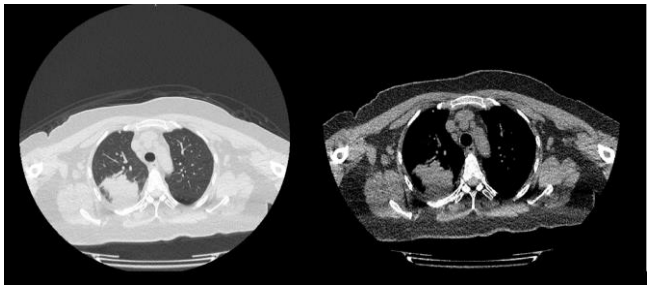

Figure 2: *Consolidated area containing air bronchograms observed in the posterior segment of the right upper lobe of the lung*

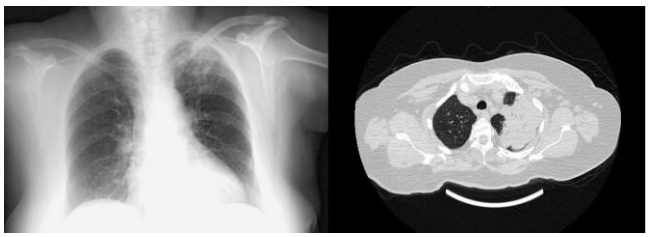

Figure 3: *Chest X-ray and thoracic CT taken 5 years earlier revealing consolidations in the left upper zone and the left upper lobe*

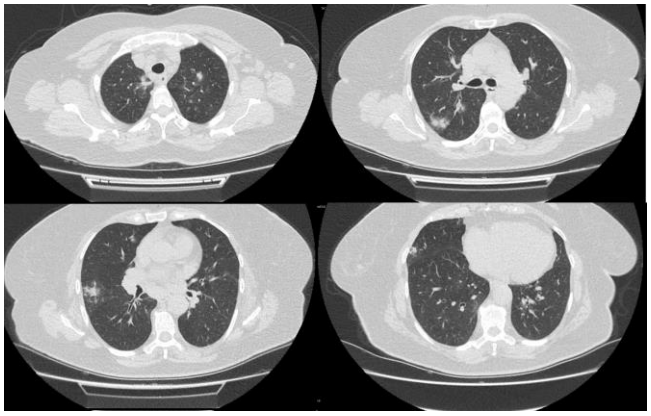

Figure 4: *Thoracic CT of the patient taken 12 months earlier revealing scattered areas of consolidation in both lungs*

CVID is the most common symptomatic primary immunodeficiency in adults. While studies generally report no gender predisposition, a recent meta-analysis of 51 studies detailing 8,521 cases reported a bimodal gender distribution, with males predominating in childhood (62%) and females in adulthood (58%). The reason for the female predominance in adults is not fully understood, although it has been suggested that sex hormone effects, epigenetic factors and environmental exposure may play a role (3–5).

CVID is typically diagnosed before adulthood, and late diagnosis in adults is relatively rare. Adult CVID is typically diagnosed after puberty, with most cases being identified between the ages of 25 and 45 years. Diagnoses in those over 65 years of age are extremely rare, accounting for only 8% of all adult CVID cases. Significant diagnostic delays can be witnessed in adulthood, as clarified by Bezrodnik et al. (6) in a study reporting an average diagnostic delay of 9.5 years in the adult population. At 68 years of age, the patient in the present study is a rare example of CVID in this age group, making the case worth reporting (7).

Impaired immunoglobulin production and inadequate antibody response to antigens due to defects in B lymphocyte differentiation form the pathophysiological basis of the disease and its predisposition to infections. Impaired immune response is most commonly blamed for frequent and severe lower and upper respiratory tract infections, as well as recurrent pneumonia. Diagnosis is based on the demonstration of hypogammaglobulinemia (IgG and IgA and/or IgM) and inadequate vaccine responses, and the exclusion of other causes of hypogammaglobulinemia (8,9).

A recent study reported the most common initial presentation of CVID to be pneumonia (36.8%), followed by diarrhea (19.1%) (10). Our patient's history of recurrent pneumonia and low immunoglobulin levels aligns with the literature in this regard.

Clinically, three different types of CVID are observed: the infectious type, characterized by an increase in the severity or frequency of infections; the autoimmune-autoinflammatory type, including such conditions as autoimmune thyroiditis and inflammatory bowel disease; and the type associated with malignancies. Autoimmune-granulomatous diseases and malignancies are more prevalent in CVID patients than in the general population. Although the exact cause has yet to be fully elucidated, the most widely accepted hypothesis is that genetic variants leading to primary immunodeficiency may directly predispose the patient to cancer, or that frequent/severe infections (oncogenic infections) may indirectly support carcinogenesis. A recent meta-analysis reported a malignancy prevalence of 8.6% in CVID, with lymphomas and gastric cancers being the most commonly associated forms (11–13), and the presence of both CVID and CLL in our case aligns with the literature in this regard. The most frequently detected microorganisms in CVID patients are encapsulated bacteria, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, resulting from defective B lymphocyte responses, and so any empirical antimicrobial therapy should cover these pathogens. The mainstay treatment is antibody replacement therapy with intravenous or subcutaneous immunoglobulin (400–600 mg/kg), typically administered once a month (14). In our case, the patient was successfully treated with both antibiotic therapy and IVIG treatment.

The increasing prevalence of HIV and the widespread use of various immunosuppressive therapies nowadays lead many patients to require immunological evaluation. Systemic disease development after live vaccination, the risk of being HIV-positive, and abnormal routine laboratory findings such as lymphopenia, neutropenia, and hypo/dysgammaglobulinemia can be observed. HIV causes progressive damage to CD4 T lymphocytes, which are vital for the maintenance of host immune response, and can lead to clinical scenarios similar to CVID, and so HIV should always be considered in adult cases of immunodeficiency. In our case, Anti-HIV was negative (15).

In conclusion, CVID should be considered even in older patients with recurrent pneumonia, and it should be kept in mind that the disease can be associated not only with recurrent infections, but also autoimmune disorders and malignancies.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - C.D., Z.Ç.; Planning and Design - C.D., Z.Ç.; Supervision - C.D., Z.Ç.; Funding - C.D., Z.Ç.; Materials - C.D., Z.Ç.; Data Collection and/or Processing - C.D., Z.Ç.; Analysis and/or Interpretation - C.D., Z.Ç.; Literature Review - C.D., Z.Ç.; Writing - C.D., Z.Ç.; Critical Review - C.D., Z.Ç.

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RESPIRATORY CASE REPORTS

Cystic Lymphangioma of the Mediastinum

Mediastenin Kistik Lenfanjioması

Mustafa Kuzucuoğlu[1], İlkay Albayrak[2], Arzu Çalık Uygun[3]

Abstract

Lymphangiomas are benign tumors originating from the lymphatic system, and it is very rare to be seen in adults and located in the mediastinum. In our study, we presented our case of mediastinal cystic lymphangioma, which we detected in a 60-year-old male patient.

Keywords: *Mediastinum, cyst, lymphangioma.*

Öz

Lenfanjiomlar lenfatik sistem kaynaklı benign tümörler olup yetişkin yaşta ve mediasten yerleşimli olarak görülmeleri oldukça nadirdir. Bizde çalışmamızda 60 yaşında erkek olguda saptadığımız mediastinal kistik lenfanjiom olgumuzu sunduk.

Anahtar Kelimeler: *Mediasten, kist, lenfanjiom.*

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Lymphangiomas are rare benign lesions originating from the lymphatic system that most commonly occur in children, and typically in the cervical region. The cystic form of lymphangioma, known also as cystic hygroma, is the most well-known type, while mediastinal lymphangiomas are much rarer, accounting for only 0.7–4.5% of all mediastinal tumors in the adult population (1-4).

We present here the case of an adult with mediastinal cystic lymphangioma, discussed in the context of relevant literature.

CASE

We describe here the case of a 61-year-old male who presented with hoarseness whose X-ray revealed no pathology, while a contrast-enhanced chest CT scan detected a lesion measuring 20x12 mm in the upper mediastinum adjacent to the aortic arch that raised suspicion for mediastinal lymphadenopathy, as well as a 7 mm nodule in the left lower lobe. A positron emission tomography (PET) scan showed no metabolic activity in the lesions, while an area of increased uptake with SUVmax: 5.3 was noted at the anterior aspect of the right 2nd rib, corresponding to a previous traumatic rib fracture (Figure 1).

The patient underwent a left anterior mediastinotomy for diagnosis and treatment during which the mediastinal lesion was excised. A histopathological examination showed positive immunohistochemical staining for D2-40, CD34 and CD31, while no reactivity was observed for CK, leading to a diagnosis of Cystic Lymphangioma (Figure 2).

Follow-up examinations in the first postoperative year reveal no recurrence or pathological findings (Figure 3).

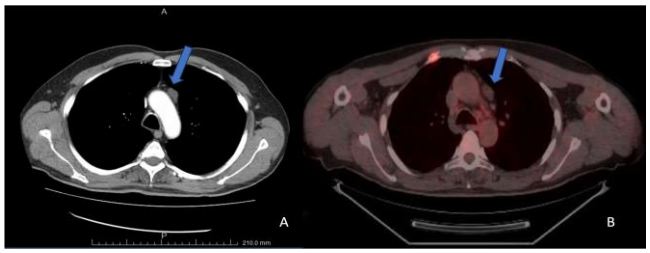

Figure 1: *Lesion identifiable adjacent to the aorta on thorax CT* ***(A)****, PET scan revealing the absence of metabolic activity in the lesion* ***(B)***

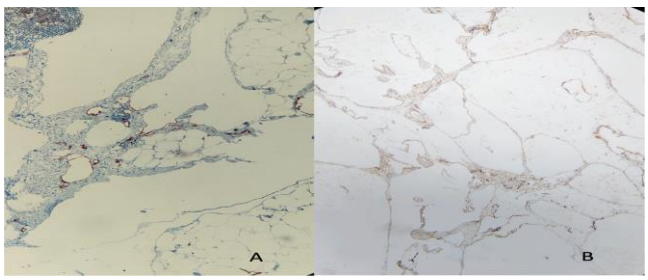

Figure 2: *Immunohistochemical examination showing lymphatic vessel structures stained with D2-40 (x5)* ***(A)****, Immunohistochemical examination showing lymphatic vessel structures stained with CD31 (x10)* ***(B)***

DISCUSSION

Lymphangiomas are rare benign lesions originating from the lymphatic system that fall under three categories: lymphangioma simplex, cavernous lymphangioma, and cystic lymphangioma (cystic hygroma). The most commonly observed cystic form is defined as a malformation resulting from a connection failure between the lymphatic and venous systems, the cause of which remains unclear. Most lymphangiomas are located in the neck and axilla, while less than 1% are found in the mediastinum (4,5).

Approximately 90% of lymphangiomas are diagnosed within the first two years of life, and around 50% are identified at birth. Such lesions are rare in adulthood and are typically asymptomatic, presenting as slow-growing masses. Mediastinal lymphangiomas are even rarer, and are usually asymptomatic and discovered incidentally (2,3,6). The presented case is a rare example of a mediastinal cystic lymphangioma.

Around 75% of cystic lymphangiomas develop in the neck, and approximately 25% in the axilla, and a very small proportion of these are located in the mediastinum, where they are often asymptomatic. Symptomatic lesions occur due to compression and can present with symptoms such as dysphagia, dyspnea, cough or chest pain (4,5). In Oshikiri et al.'s (2) study of five cases of mediastinal lymphangiomas, four of the cases were asymptomatic, while the other presented with superior vena cava syndrome resulting from compression. Similarly, the cases described by Saleiro et al. (3), Suehisa et al. (5) and Zhou et al. (7) all had asymptomatic mediastinal cystic lymphangiomas. In contrast, dyspnea and wheezing were observed in the case presented by Rali et al. (8). In our case, the patient presented with hoarseness, which is a relatively uncommon symptom in mediastinal lymphangiomas.

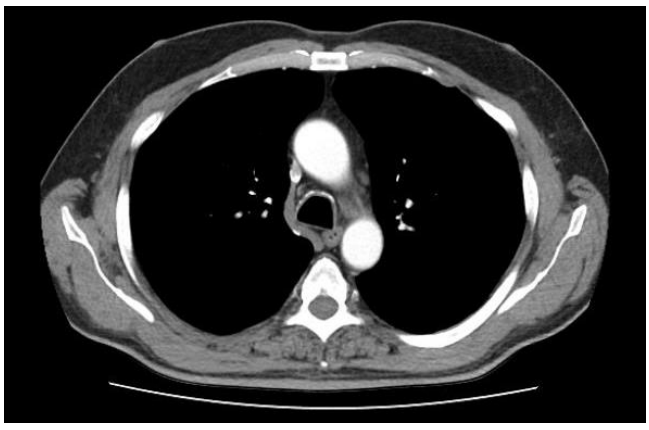

Figure 3: *Thorax CT appearance at 1-year postoperative follow-up*

Mediastinal cystic lymphangiomas are often discovered incidentally through radiological imaging. Chest X-rays

typically do not reveal specific lesions, although larger lesions may be seen as well-defined, round-shaped mediastinal enlargements. Both Thorax Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are effective in detecting mediastinal lymphangiomas. While chest CT is more commonly used and can help determine the size, density and location of a lesion, it is unreliable for definitive diagnosis. Furthermore, while chest MRI can reveal the heterogeneity of cystic components and the intense vascularization of lesions, it is also not conclusive for diagnosis. The optimum approach to definitive diagnosis is surgical excision followed by histopathological examination (3–5). In our case, the chest CT revealed a well-defined, homogeneous lesion in the mediastinum. Although unprecedented in the literature, we also performed a positron emission tomography (PET) scan, which revealed no metabolic activity in the lesion. As a definitive diagnosis could not be made radiologically, we proceeded with surgical resection for diagnosis and treatment.

Histopathological examinations of mediastinal cystic lymphangiomas typically show immunohistochemical staining for CD31, and D2-40 positivity in the lymphatic vessels within the lesion (5). In our case, the excised mass showed positive staining for both CD31 and D2-40, based on which the diagnosis was confirmed.

Surgical excision is considered the optimum treatment choice for lymphangiomas, and complete excision of the lesion is recommended to prevent recurrence. Recent studies have shown video-assisted thoracoscopic surgery (VATS) to be successful in mediastinal lymphangiomas (4,5,7). Although VATS has emerged as the first-choice surgical method in recent years, especially for mediastinal masses, we opted for an anterior mediastinotomy approach in our case as we felt more comfortable with the procedure.

In conclusion, although cystic lymphangiomas are frequently congenital and present in the neck region in childhood, the possibility of mediastinal lymphangiomas should also be considered in adults. Once diagnosed, lesions should be excised surgically to avoid complications and recurrence.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - M.K., İ.A., A.Ç.U.; Planning and Design - M.K., İ.A., A.Ç.U.; Supervision - M.K., İ.A., A.Ç.U.; Funding - M.K., İ.A., A.Ç.U.; Materials - M.K., A.Ç.U.; Data Collection and/or Processing - İ.A.; Analysis and/or Interpretation - M.K.; Literature Review - M.K.; Writing - M.K., A.Ç.U.; Critical Review - M.K.

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Organizing Pneumonia: Three Case Reports

Organize Pnömoni: Üç Olgu Sunumu

Coşkun Doğan, Göksel Menek

Abstract

Organizing pneumonia is characterized histopathologically by the accumulation and proliferation of fibroblasts, myofibroblasts and collagen within the alveolar and bronchiolar lumens, with such potential causes as drug reactions, radiation therapy, collagen vascular diseases and infections. In cases with a specific cause, the condition is referred to as secondary organizing pneumonia, and cryptogenic organizing pneumonia when no cause is apparent. Radiologically, nodules or mass lesions accompanied by air bronchograms may be observed together with patchy peripheral alveolar consolidations. Although not present in every case, the reverse halo sign is an important radiological finding. While clinical-radiological diagnosis is possible, it must be confirmed histopathologically. When steroids appropriate dosages and durations are applied, the results are usually outstanding.

Keywords: *Bronchiolitis Obliterans, organising pneumonia, halo sign.*

Öz

Histopatolojik tanım olarak Organize Pnömoni (OP), alveolar alanlar ve bronşiol lümen içinde fibroblastların, miyofibroblastların ve kollagenin toplanması aynı zamanda proliferasyonu ile karakterize bir akciğer hastalığıdır. OP'ye başta ilaç reaksiyonları, radyasyon tedavisi gibi etkenler olmak üzere, kollajen vasküler hastalıklar, enfeksiyonlar gibi birçok hastalık neden olabilir. Radyolojik olarak hava bronkogramlarının eşlik ettiği nodül veya kitle lezyonlar ile birlikte periferik, yamalı alveolar konsolidasyonlar görülebilir. Her olguda görülmemekle birlikte ters halo işareti önemli bir radyolojik bulgudur. Tanısı klinik-radyolojik ve histopatolojik yöntemler ile konulur. OP tedavisinde uygun doz ve sürede kullanılan glukokortikoid tedaviye yanıtları çok iyidir.

Anahtar Kelimeler: *Bronşiolit Obliterans, organize pnömoni, halo işareti.*

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Organizing pneumonia (OP), referred to previously as bronchiolitis obliterans organizing pneumonia (BOOP), is a histopathological condition characterized by an accumulation and proliferation of fibroblasts, myofibroblasts and collagen within the alveolar and bronchiolar lumens. In cases where the underlying etiology is unclear, the condition is classified as cryptogenic organizing pneumonia (COP). Conversely, if a causative factor is identified, it is referred to as secondary organizing pneumonia (SOP). SOP in particular has been associated with autoimmune diseases, infections, malignancies, specific medications and radiation exposure (Table 1) (1-3).

This report contributes to OP literature by presenting three cases diagnosed during outpatient evaluation in a pulmonary clinic, two of which were confirmed through histopathological examination, while the third was diagnosed based on clinical and radiological findings.

CASE

Case 1: A 65-year-old female patient with a known history of hypertension (HT) and asthma presented to the pulmonary clinic with complaints of cough, sputum production, back pain, night sweats and weight loss (10 kg over 2 months). A posteroanterior chest X-ray (PA CXR) revealed an irregularly marginated opacity in the paracardiac area of the right lower zone (Figure 1A), while physical examination findings were unremarkable. Laboratory tests produced the following results: WBC: 7.5 x $10^3/\mu l$, serum C-reactive protein (CRP): 67 mg/dL and erythrocyte sedimentation rate: 18 mm/hour, and spirometry and carbon monoxide diffusion capacity (DLCO) measurements were as follows: FEV1/FVC: 98 %, FEV1: 1.26 L (80%), FVC: 1.97 L (72%), DLCO: 24.72 mL/min/mmHg (73%), and DLCO/VA: 4.55 mL/min/mmHg/L (82%). A thoracic computed tomography (CT) scan performed after 1 week of oral 2x500 cefuroxime axetil and 2 weeks of 2x500 oral clarithromycin revealed a consolidated area with air bronchograms in the paravertebral region of the superior segment of the right lower lobe (Figure 1B).

The persistency of the findings on follow-up PA CXR led us to carry out a CT-guided tru-cut biopsy (CT-TCB), and a histopathological examination of the sample revealed a fibroblastic proliferation within the alveolar lumens and interstitial areas with a loose fibromyxoid matrix. The alveolar lumen was filled with a histiocytic infiltration, accompanied by prominent lymphoid aggregates, and chronic inflammatory cell infiltration was identified along with mild fibrosis in the bronchial wall. The patient was diagnosed with OP and started on methylprednisolone 40 mg daily.

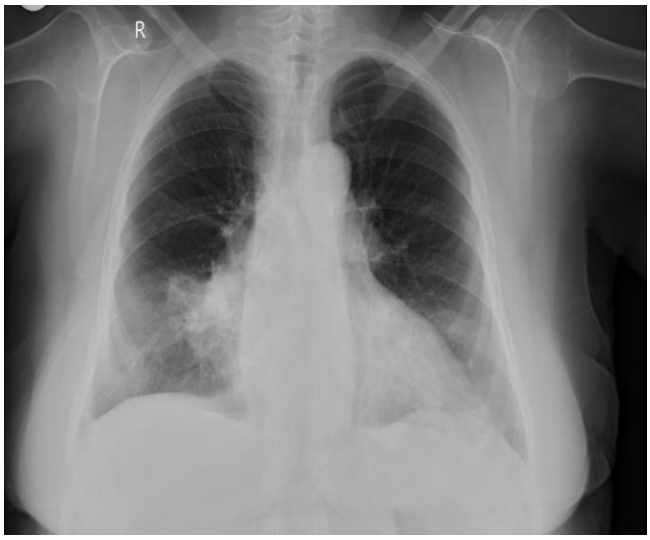

Figure 1a: *An irregularly bordered, non-homogeneous increased density in the paracardiac area of the right lower lung zone*

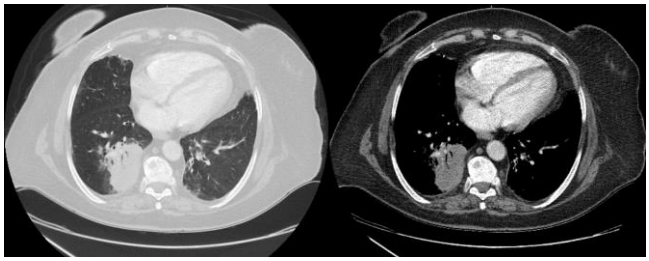

Figure 1b: *An irregularly bordered, non-homogeneous increased density in the paracardiac area of the right lower lung zone*

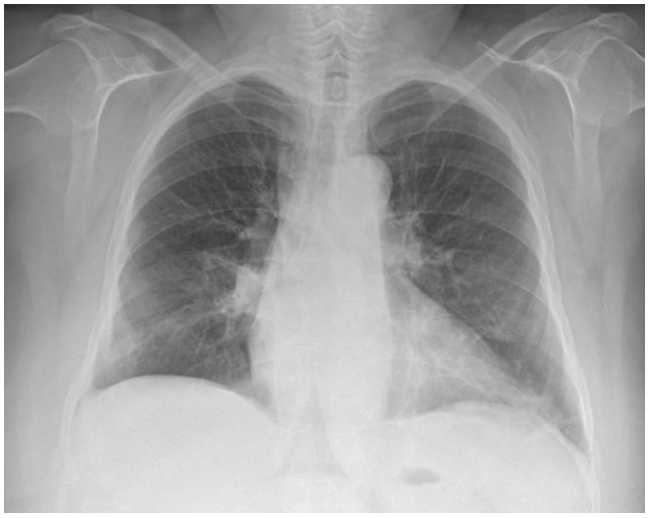

Figure 1c: *Significant regression noted on follow-up chest X-ray*

The methylprednisolone treatment was gradually reduced and terminated after a total of 3 months. Significant regression was observed following the first month of treatment (Figure 1C).

Table 1: Causes of Cryptogenic Organizing Pneumonia and Secondary Organizing Pneumonia

Diseases	Diseases that can cause Organizing Pneumonia
Autoimmune Diseases	•RA, DM-PM, SS, SD, AS, SLE •Behcet Disease, Mixed Cryoglobulinemia, PAN •Inflammatory Bowel Diseases
Other Diseases	• ARDS, Chronic Eosinophilic Pneumonia • SIP-UIP, Cystic Fibrosis, CVID • Emphysema, Bronchiectasis, Sarcoidosis • CHF - CKD, Coronary Bypass Grafts
Neoplasms	• Lung and GI malignancies • Hematological Malignancies
Infectious Diseases • *Viral* • *Bacteria* • *Fungal* • *Others*	• HIV, Adenovirus, Influenza and Parainfluenza • SARS-CoV-2, SARS-CoV, MERS-CoV • Mycoplasma sp, Chlamydia sp, Legionella pneumophila • Streptococcus pnumoniae, Staphylococcus aureus • Actinomyces israelii, Serratia sp, Nocardia sp. • Aspergillus sp, Pneumocystis jirovecii • Cryptococcus neoformans, Penicillium sp. • Plasmodium vivax
Transplantation	• Solid organ transplants (includes lungs)
Others	•Toxic gases, Cocaine-Cannabis Inhalation, electronic cigarette
Drugs	**Drugs that can cause Organizing Pneumonia**
Antibiotics	• Minocycline, Nitrofurantoin • Cephalosporins, Amphotericin
Antiarrhythmics	• Amiodarone, Beta blockers • Phenytoin, Hydralazine, Timolol
Biological Agents	• Interferons, Trastuzumab, Rituksimab • Bortezomib, Ceritinib • Tosilizumab, Etanersept, Infliximab, Ipilimumab
Kinase Inhibitors	• Sirolimus, Everolimus • Anti EGFR, Anti ALK inhibitors
PD-1/PD-L1 Inhibitors	• Pembrolizumab, Atezolizumab, Nivolumab
CT-RT	• Azathioprine, Chlorambucil, Cladribine • Bleomycin, Busulfan, Mitomycin • Methotrexate, Doxorubicin, Daptomycin • Oxaliplatin, Thalidomide
Others	• Statins, Dihydroergocryptine, Penicillamine • Propylthiouracil, Carbamazepine

Case 2: A 48-year-old female patient with a history of pancreatic cancer surgery approximately 10 years earlier, followed by one year of chemotherapy, presented with complaints of cough, hemoptysis and chest pain. A posteroanterior chest X-ray (PA CXR) obtained at the referring center revealed a peripheral density in the right upper zone (Figure 2A). Physical examination findings were unremarkable. Laboratory test results were as follows WBC: 12 x 10^3/μL, hemoglobin (Hb): 10.7 g/dL, CRP: 37.1 mg/dL and erythrocyte sedimentation rate: 16 mm/hour.

Spirometry revealed FEV1/FVC: 77 %, FEV1: 2.08 L (79%), and FVC: 1.98 L (67%). The patient was unable to cooperate with the DLCO test. Thoracic computed tomography (CT) scans from two different centers with a short interval between revealed migratory and transient lesions (Figure 2B). Metastatic disease was initially suspected given the patient's history of pancreatic cancer, and so a CT-guided tru-cut biopsy (CT-TCB) was performed. The pathology report described intraluminal granulation tissue within the bronchioles, cellular infiltration in the interstitium, alveolar septal inflammation, and intra-alveolar cellular desquamation with a small amount of granulation tissue, and histopathological findings were consistent with OP. The patient was started on methylprednisolone at a dose of 0.5 mg/kg, but she opted to discontinue the treatment on the third day. Follow-up chest X-rays revealed a significant regression of the lesions. The patient was subsequently managed without treatment and followed up with a diagnosis of OP exhibiting spontaneous regression (Figure 2C).

Case 3: A case with known nodular sclerosis Hodgkin lymphoma (NSHL) who was undergoing chemotherapy was referred to the Chest Diseases outpatient clinic due to new-onset shortness of breath and cough complaints. The PA CXR revealed peripheral opacities in the bilateral upper zones and widespread non-homogeneous opacities in the middle and lower zones (Figure 3A). A physical

examination identified crackles in the bilateral lower fields, and the laboratory parameters showed WBC: $3.1x10^3/\mu l$, CRP: 2 mg/dl, and Sedimentation: 12 mm/hour. The patient was subsequently started on oral 2x500 cefuroxime axetil and oral 2x500 clarithromycin, however, the patient's symptoms did not improve following the first week of antibiotic therapy. A direct examination of sputum for acid-resistant bacilli (ARB) yielded a negative result, and no growth was observed in the culture. Thoracic CT revealed widespread nodular opacities in the bilateral lungs (Figure 3B) and opacity compatible with a reverse halo sign in the right lung (Figure 3C). Spirometry findings were FEV1/FVC: 77 %, FEV1: 3.42 L, 118%, FVC: 3.88 L, 131%, DLCO: 21.30 L, 76%, and DLCO/VA: 5.05 L, 99%. The case was started on 40 mg of methylprednisolone treatment with a clinical radiological diagnosis of OP, and complete regression was observed by the third month of treatment (Figure 4).

DISCUSSION

Organizing pneumonia (OP) is a benign condition that, due to its radiological and histological characteristics, often requires differentiation from lung malignancies. OP is a rare clinical entity that, by nature, is diagnostically challenging. The diagnostic process for OP begins with suspicion of the disease based on the patient's clinical presentation and the clinician's judgment, and should be considered in differential diagnosis.

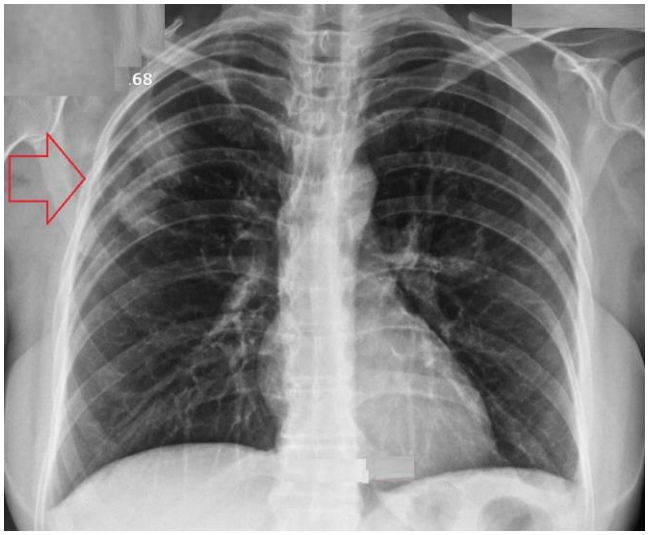

Figure 2a: *Non-homogeneous density located peripherally in the upper zone of the right lung*

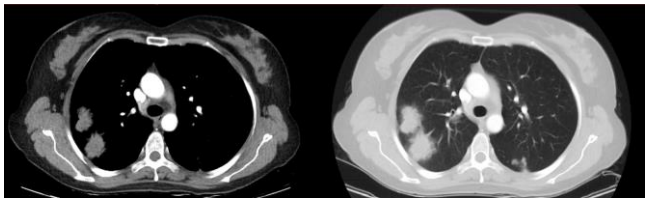

Figure 2b: *Thoracic CT showing two lesions with soft tissue densities in the right upper lung lobe*

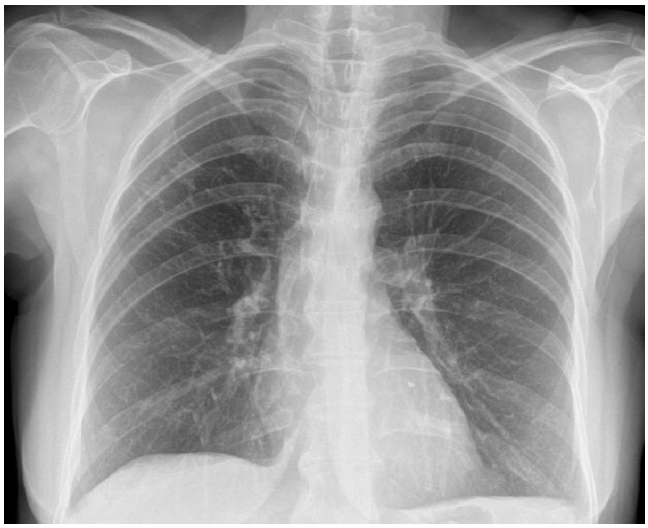

Figure 2c: *Significant regression noted on follow-up chest X-ray*

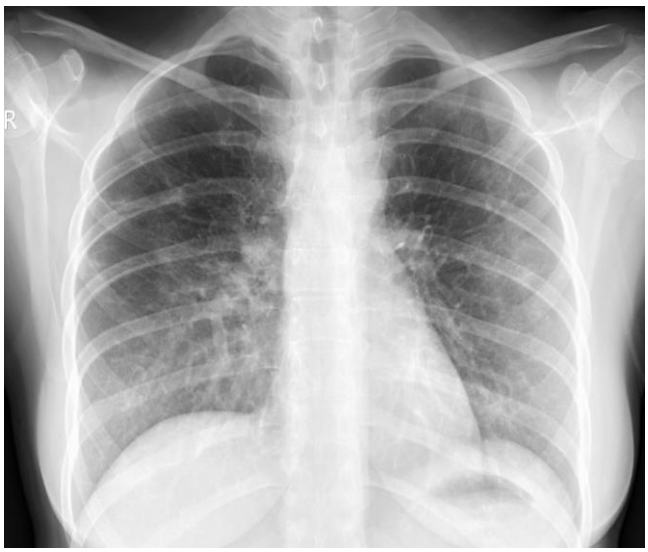

Figure 3a: *Chest X-ray revealing peripheral involvement in the bilateral upper zones and widespread non-homogeneous densities in the mid-lower zones*

The clinical findings, laboratory results, symptoms and signs of OP are typically non-specific. Physical examination (PE) may be normal in 25% of cases, although inspiratory rales are frequent findings. Laboratory markers specific to OP are lacking, although approximately 50% of cases show elevated levels of such non-specific inflammatory markers as white blood cell count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Commonly observed symptoms in OP include dry cough, flu-like symptoms, exertional dyspnea, fever, fatigue and weight loss, while hemoptysis is less frequently seen. In cases where clinical and radiological findings align, spirometry and a diffusion capacity for carbon monoxide (DLCO) test may assist in diagnosis, often revealing mild-

to-moderate restrictive patterns and a reduction in diffusion capacity (4,5). Rales were identified only in the third of the presented cases, while the first two cases had normal physical examination findings. Cough was a common symptom in all three cases, while hemoptysis was noted in one case and weight loss in another, as symptoms that are less frequently reported in OP. Concurring with previous studies in the literature, the pulmonary functions test results of all cases indicated mild restriction, while mild reductions in diffusion capacity were identified in two of the presented cases.

OP is a disease that affects the lung interstitium, and so as would be expected, typically presents with mild decreases in FVC and DLCO. Studies have shown that SFT-DLCO values may not decrease dramatically in all cases despite radiological intervention, with 30% of OP cases exhibiting normal SFT-DLCO values, and mild reductions noted in 60–70% of cases (6). The most accurate radiological diagnoses of OP are through thoracic computed tomography (CT) or high-resolution CT (HRCT), multifocal consolidations with air bronchograms being apparent in the latter. Other possible findings include peripheral patchy alveolar consolidations, nodules, ground-glass opacities, bronchial wall thickening and reticular fibrous changes. One rare but significant finding on HRCT is the reverse halo sign (Atoll Sign), which was first described in OP referring to a focal ground-glass opacity surrounded by a ring-like consolidation (2,7,8). In the first of our cases, thoracic CT revealed characteristic air bronchograms, while the second case exhibited peripheral multifocal consolidations and the reverse halo sign was noted in the third case.

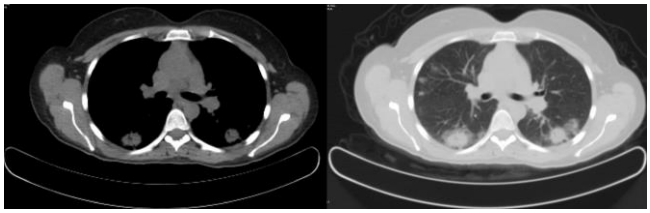

Figure 3b: *Thoracic CT showing widespread nodular opacities in both lungs*

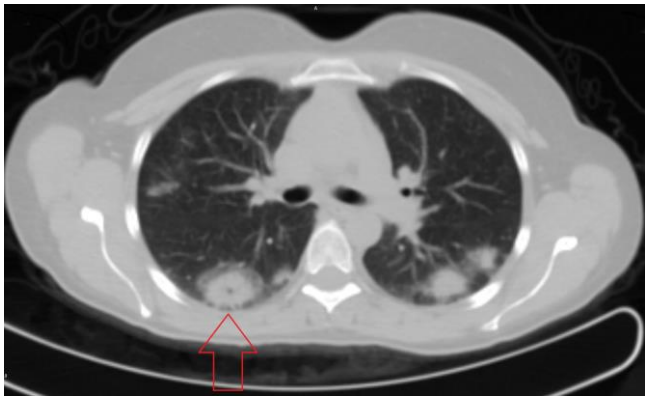

Figure 3c: *Thoracic CT showing widespread nodular opacities in both lung*

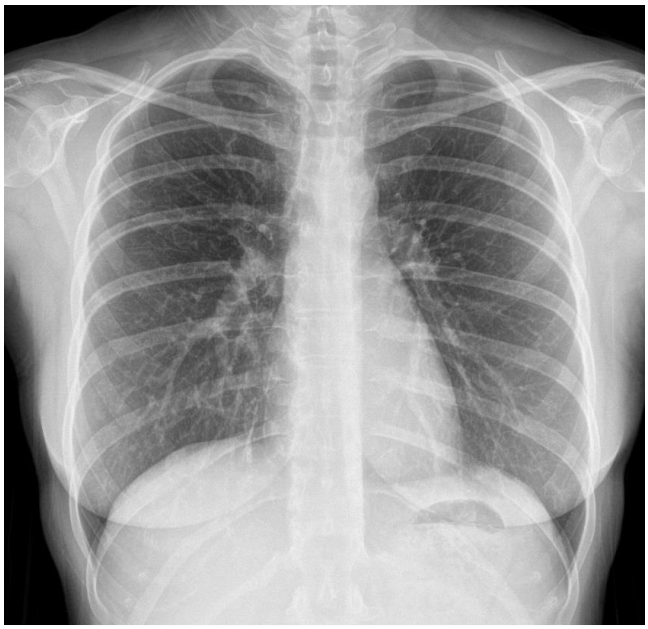

Figure 4: *Complete regression shown on Lung Radiograph*

An examination of the histopathological findings of cases with organizing pneumonia (OP) revealed the most common findings to be intraluminal granulation tissue (Masson bodies) within the bronchioles, which are small airways, mononuclear cell infiltration in the interstitium, and intra-alveolar cellular desquamation. The most common consolidations detected radiologically are, in fact, formed histopathologically from intra-alveolar fibroblastic granulation tissue, known also as Masson bodies. Similarly, ground-glass opacities observed radiologically correspond histologically to alveolar septal inflammation and areas of intra-alveolar cellular desquamation with small amounts of granulation tissue in the terminal airspaces (9). The diagnoses of our first two cases were established based on histopathological methods, as their histopathological findings were consistent with OP.

Today, the mainstay of treatment for OP is glucocorticoids, and response is typically rapid and favorable in patients without respiratory failure and with a good general clinical condition. The optimal glucocorticoid regimen and treatment duration have yet to be determined, but the most commonly approach is to administer prednisone at a dose of 0.5–1 mg/kg daily for 6–12 months, with tapered doses over time. In cases of severe OP with respiratory failure, high-dose/pulse steroids (e.g., 500–1000 mg of methylprednisolone followed by maintenance therapy with 1 mg/kg oral methylprednisolone) and other immunosuppressive agents may be used. Additionally, macrolide antibiotics may be employed due to their anti-inflammatory effects, and surgical treatment may be considered for localized OP (10,11). Spontaneous regression without treatment is observed in approximately 10% of

OP cases, and while the exact mechanisms behind this regression remain unclear, there are studies suggesting a link to specific clinical and laboratory results. Spontaneous regressions of OP may be attributable to such temporary factors as viral infections or inhalation injury, and to lower serum CRP levels and higher lymphocyte counts at the time of diagnosis (12). In our series, the first and third cases responded well to methylprednisolone treatment, while the second exhibited spontaneous regression.

In conclusion, OP is a disease with a typically subacute clinical course. The presence of such radiological features as nodules and masses can lead OP to be mistaken for lung malignancies, making it essential to consider it in differential diagnosis. The clinical and radiological characteristics of OP, as well as the treatment approaches presented in the three presented cases, emphasize the need to keep this condition in mind in clinical practice.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - C.D., G.M.; Planning and Design - C.D., G.M.; Supervision - C.D., G.M.; Funding - G.M.; Materials - G.M.; Data Collection and/or Processing - C.D.; Analysis and/or Interpretation - C.D.; Literature Review - G.M.; Writing - C.D.; Critical Review - C.D.

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Warfarin-Induced Hepatotoxicity: A Case Report

Warfarine Sekonder Gelişen Hepatotoksisite: Olgu Sunumu

Çiğdem Sabancı, Sida Gösterici, Hülya Abalı, Aysun Temel Incebacak, Fatma Tokgoz Akyil

Abstract

A 30-year-old male patient with no comorbidities was admitted to hospital after developing a pulmonary embolism and was started on warfarin treatment. His hepatic enzymes increased progressively. In the early period after warfarin, an elevated liver function test was observed on the 4th day. Hepatotoxicity was thought to have developed secondary to warfarin, and the enzymes decreased gradually after the warfarin treatment was discontinued. We present this case as evidence of the possible development of hepatotoxicity secondary to warfarin treatment, even in the early period of treatment, and to discuss the management and follow-up outcomes of such patients.

Keywords: *Hepatotoxicity, pulmonary embolism, warfarin.*

Öz

Otuz yaşında, bilinen ek hastalığı olmayan erkek hasta pulmoner emboli tanısı ile kliniğimize yatırıldı. Takibinde varfarin tedavisi başlanan hastada tedavinin dördüncü gününde karaciğer fonksiyon testlerinde yükseklik izlendi. Diğer nedenler dışlanarak varfarine sekonder hepatotoksisite tanısı konulan hastanın varfarin kesildikten sonra değerlerinde kademeli düşüş izlendi. Bu olgu sunumunun amacı, varfarin tedavisine sekonder görülen hepatotoksisitenin, tedavinin erken döneminde de gelişebileceğini hatırlatmak, bu hastaların yönetimi ve takibinin tartışılmasıdır.

Anahtar Kelimeler: *Hepatotoksisite, pulmoner emboli, varfarin.*

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Thromboembolic conditions are responsible for one in four deaths worldwide, among which pulmonary embolism (PE), one of the major thromboembolic conditions, has an incidence ranging from 39 to 115 per 100,000 population/year (1). Acute PE ranks third on the list of the most prevalent cardiovascular diseases, following coronary artery disease and stroke (2).

Warfarin therapy, despite its narrow therapeutic index and wide range of responses, continues to be a common approach to the treatment of thromboembolic disease in various clinical settings. Oral anticoagulants such as vitamin K antagonists (VKAs) which include warfarin (Coumadin), acenocoumarol and phenprocoumon, are considered safe options to the point that they have for many years been considered the optimum treatment (3) The most preferred and widely used of the VKAs is "warfarin sodium", which acts mainly by inhibiting the synthesis of the coagulation factors of prothrombin (factor II), factor VII, factor IX and factor X, in the liver, thus intervening into the vitamin K cycle (4).

As the response to warfarin therapy is extremely volatile among patients, optimal dosing is key. One serious adverse effect of warfarin is excessive bleeding, while other side effects include nausea, vomiting, abdominal pain, bloating, flatulence and changes to the sense of taste. Rarer side effects include purple finger syndrome, skin necrosis and calciphylaxis (5,6). Warfarin requires cautious monitoring as it elevates transaminases levels in 0.8–1.2 of cases%. Once hepatotoxicity develops close monitoring is simply required and clinical management may be difficult. There are reports of cases developing fulminant liver failure secondary to warfarin treatment, but most frequently in older adults (7,8).

We present here the case of a young male patient who developed warfarin-related hepatotoxicity in the early treatment period.

CASE

A 30-year-old male patient was admitted to our emergency department with complaints of increasing left-sided back pain for four days and hemoptysis. The patient had undergone a lumbar disc herniation operation in the previous month. He was employed as a long-distance driver and had an ongoing smoking history of 23 pack/years.

Physical examination, respiratory sounds and vital signs were normal. Among the laboratory parameters at admission, C-reactive protein (CRP) was 19.8 mg/L (N: 0-5) and leukocyte was 10.6 103/µl (N: 7-10 103), while all other hemogram and biochemistry parameters were within the normal range. No abnormal findings were observed on postero-anterior chest radiography (Figure 1).

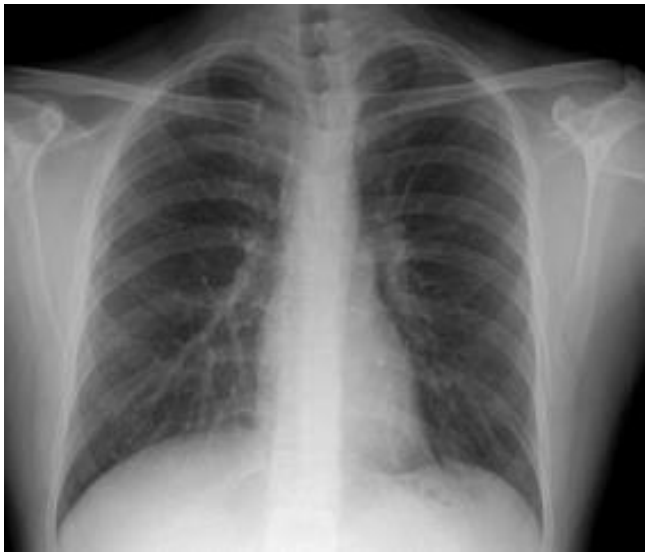

Figure 1: *Chest X-ray at admission*

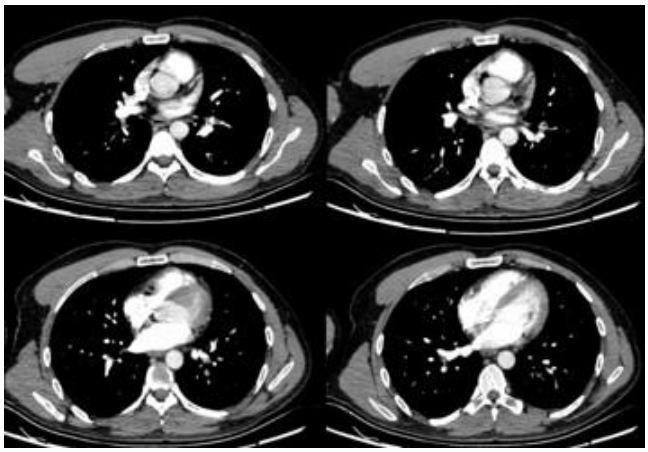

Figure 2: *Thorax computed tomography at admission showing thrombus in the left lower lobe pulmonary artery*

Our patient's troponin level was 5.09 ng/l and pro-brain natriuretic protein level was 17 pg/ml and was within the normal range. The patient's Wells Score indicated a medium clinical probability of pulmonary embolism.

Despite the normality of the patient's findings, PE was considered due to the patient's recent surgery, and his employment as a long-distance driver, hemoptysis history and D-dimer of 2.54 µg/ml (0–0.5). A thoracic computed tomography angiography (CTA) requested for further examination revealed a filling defect consistent with thrombus in the left lower lobe pulmonary artery (Figure 2).

The patient was admitted to our clinic and started on enoxaparin 8000 iu/0.8 ml 2*1, cefuroxime 500 mg 2*1 po and symptomatic treatments. Electrocardiography (ECG) revealed an incomplete right bundle branch block, but no evidence of right heart failure on 108/min echocardiography. A Doppler ultrasonography of the lower extremities revealed no deep vein thrombosis in the acute phase. No hemoptysis was noted during follow-up at that point, and 5 mg warfarin was added to the therapy on

the fifth day. The enoxaparin was discontinued on the third day of treatment after the INR (international normalized ratio) was noted to have risen to 2.2. Liver function tests were also conducted revealing alanine aminotransferase (ALT): 163 (N: 0-40) U/L; aspartate aminotransferase (AST): 109 (N: 0-40) U/L; and bilirubin values within normal limits. Antibiotics and other symptomatic treatments were discontinued and intravenous hydration therapy was started, and the treatment was discontinued the following day after the patient's liver function values increased the following day. The probability of secondary hepatic toxicity from warfarin was almost certain by that time, and so enoxaparin treatment was considered the first choice (Figure 3). The patient's physical examination and abdominal ultrasonography were normal. Contrast-enhanced abdomen CT, and hepatitis and autoimmune hepatitis marker tests [anti-nuclear antibody, anti-double strand-DNA, anti-liver-kidney microsomal antibody tests (anti-LKM), and anti-mitochondrial antibody (AMA)] amylase and lipase tests were requested by the internal medicine specialist, along with treatment with hepatamine, N-acetyl cysteine and hydration support containing vitamins. The liver function test results started to decrease after the third day of follow up. Radiological imaging was unremarkable other than the identification of a hiatal hernia. The internal medicine physician recommended no further treatment, and so the patient was discharged upon their own request on the condition that he would return for a check-up 2 days later while his liver enzymes were AST 116 U/L and ALT 492 U/L, planning to continue treatment with low molecular weight heparin treatment until his LFT returned to normal range.

Liver enzymes, which usually start to decrease 11 days after the discontinuation of warfarin treatment, started to increase again on the 11th day after discontinuation, the cause of which was unknown, and the patient's liver enzymes were observed to have decreased again by the time of the next control.

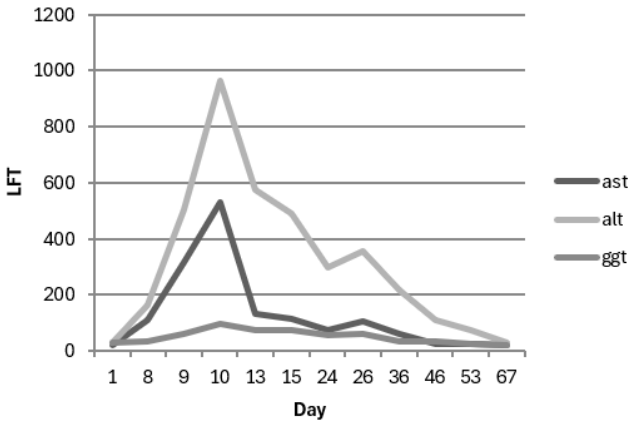

Figure 3: Follow-up results of liver function tests after the initiation of warfarin treatment

The patient's LFT values were recorded to be within the normal range during outpatient clinic follow-ups. There is no clear suggestion of how long it takes for the liver enzymes to return to normal in cases of hepatotoxicity secondary to warfarin.

The patient declined subcutaneous treatment, and so treatment with dabigatran 150 mg twice daily was initiated, with no side effects or laboratory abnormalities noted on follow up.

A thrombophilia panel in the third and fourth month of follow-up revealed a decrease in protein S activity to 45% and 33% (77–143) and a total protein S antigen of 55.7% (60-130). Consultation with the hematology department led to the continuation of oral anticoagulants. The patient remains stable under dabigatran treatment in the second year of treatment.

DISCUSSION

Warfarin is a widely used oral anticoagulant that exerts its influence through an anti-vitamin K activity mechanism. Acute liver injury typically occurs within 3–8 weeks of starting warfarin therapy. Though rare, cases of liver injury occurring after months or years of treatment have also been reported (9).

Similar to our case, a 79-year-old female patient who developed hepatotoxicity in the first week of warfarin treatment has been reported in the literature. In this case, LFTs were normal prior to treatment, and started to increase 6 days after the initiation of warfarin treatment for deep vein thrombosis (DVT) (10). This case has similarities with our presented case, as in both cases the patient suffered liver damage within a week of starting warfarin treatment, which is a notably rare occurrence. In the example above, the patient's LFTs returned to within the normal range 3 days after the discontinuation of warfarin, compared to approximately 2 months in the presented case, despite the young age profile of the patient. This wide discrepancy, we believe, merits attention.

While the exact cause of liver injury in cases undergoing oral anticoagulant therapy remains unknown, it is safe to assume that the fundamental causation is mainly immunological (9). A recent study in mice identified four primary mechanisms with the potential to explain the hepatotoxicity in oral warfarin administration: i) CYP2C9 regulation affecting the amount of bleeding, depending on nuclear factor erythroid 2-related factor 2 (NRf2) and P450 levels, ii) a fall in NRf2 leaving the system open to oxidative stress, increasing the likelihood of bleeding, iii) decreased hemoglobin, albumin and antitrypsin levels leading to apoptosis liver hemorrhage, apoptosis and fibrosis by activating cleaved caspase-3, and 4) warfarin elevating transferrin levels and lipid peroxidation with pro-fibrogenic stimuli, leading to fibrosis and acute liver damage with higher iron level and hemosiderin (11).

Since our hospital is not a multidisciplinary center and no liver biopsy was performed, the mechanism of hepatotoxicity could not be ascertained.

Patient liver enzyme elevation patterns are typically cholestatic, although hepatocellular and mixed patterns have also been reported. Eosinophilia may also be encountered, while other immunoallergic manifestations and autoantibodies are less common.

Elevated ALT or AST in patients using anticoagulants make differential diagnosis challenging. The optimum diagnostic approach is liver biopsy, however, its invasiveness bears high risk potential (12). The first step in the evaluation of elevated ALT or AST levels a repeat of laboratory tests, and if the results are still abnormal, conditions such as alcohol use, hepatotoxic drugs, chronic hepatitis B and C, autoimmune hepatitis, nonalcoholic fatty liver disease, hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency and celiac sprue should be considered (13). If the increasing trend is still not stemmed, switching to another class of anticoagulant agent is supported in the literature. The immediate termination of anticoagulant therapy may also be considered, especially if bilirubin levels are higher than twice the normal range. Fulminant liver failure may develop within two weeks of the onset of hepatocellular damage (12).

One noteworthy feature in our patient profile was the protein S deficiency, which has been reported to have potential links to hepatotoxicity (14). As our case confirmed this relationship, we believe that more detailed research is warranted as elucidating the mechanisms of hepatotoxicity will clarify if any relationship exists with the toxic mechanism of the drug, or whether the relationship is purely coincidental.

Dabigatran has been shown to be as effective as warfarin in patients with thrombophilia (15,16), while apixaban and rivaroxaban have been reported to be safe in small case series (17). No bleeding or recurrent thrombosis was identified in our patient while under dabigatran treatment for 1 year, leading us to consider dabigatran to be another safe option in such cases.

In contrast, apixaban should be avoided in patients with warfarin-induced cholestasis, although existing research is not unambiguous, and further studies are needed to determine the optimum agents for anticoagulant-induced hepatotoxicity (10). Our case was continued on low molecular weight heparin until the liver enzymes returned to normal, after which he was switched to dabigatran treatment with close monitoring. Independent of warfarin hepatotoxicity, hepatotoxicity under dabigatran treatment was reported in an 84-year-old patient, although the mechanism was thought to have other bases and interactions since the drug has no effect on the cytochrome P450 enzyme (18). Since our patient was young and declined subcutaneous treatment, we opted for dabigatran treatment with close clinical and laboratory follow-up, and he has remained stable throughout his 1-year follow-up.

There are limited resources in the literature reporting on protein C and protein S deficiencies. An article published in China in 2024 reported on a patient who presented with acute liver failure due to protein C deficiency (19).

The mechanism of liver damage attributable to warfarin could not be further determined since no liver biopsy could be performed.

In conclusion, hepatotoxicity secondary to warfarin may develop rapidly while laboratory recovery may catch up lately. Although our patient's condition was rendered stable with dabigatran treatment, more case reports and clinical studies are needed to better understand the mechanisms of hepatotoxicity to identify safer and more appropriate treatment choices.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - Ç.S., S.G., H.A., F.T.A., A.T.I.; Planning and Design - Ç.S., S.G., H.A., F.T.A., A.T.I.; Supervision - Ç.S., S.G., H.A., F.T.A., A.T.I.; Funding - Ç.S.; Materials - Ç.S.; Data Collection and/or Processing - Ç.S.; Analysis and/or Interpretation - Ç.S.; Literature Review - Ç.S.; Writing - Ç.S., F.T.A.; Critical Review Ç.S., F.T.A.

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