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Case Report

Pathology Section

Pulmonary Artery Intimal Sarcoma: Unmasking a Rare and Lethal Mesenchymal Malignancy Mimicking Thrombus

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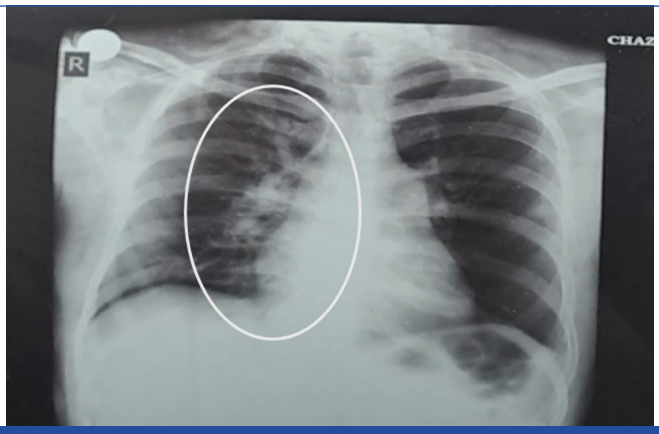
ABSTRACT

Pulmonary Artery Intimal Sarcoma (PAIS) is an aggressive, rare, and lethal malignant tumour arising from pluripotent mesenchymal cells in the pulmonary artery intima. It is an uncommon neoplasm that is frequently misdiagnosed because of its clinical and radiological resemblance to pulmonary thromboembolism. We report the case of a 29-year-old male who presented with right-sided chest pain, cough, and exertional dyspnoea of two weeks' duration, with stable vital signs at presentation. Imaging studies such as roentgenography and CT thorax favour the diagnosis of pulmonary embolism. Patient underwent thrombolysis and failed. Further investigations, including anti-thrombin III, protein C, protein S, lupus anticoagulant, D-dimer, and bilateral lower limb venous Doppler studies, were performed to evaluate the cause of pulmonary embolism; however, all results were unremarkable. As the symptoms persist patient underwent pulmonary endarterectomy. Histopathological examination revealed an undifferentiated malignant mesenchymal neoplasm arising from the pulmonary artery intema. Immunohistochemical analysis demonstrated diffuse vimentin positivity, confirming mesenchymal origin, along with strong nuclear MDM2 positivity, supporting the diagnosis of PAIS. Negative staining for endothelial markers helped exclude vascular neoplasms.

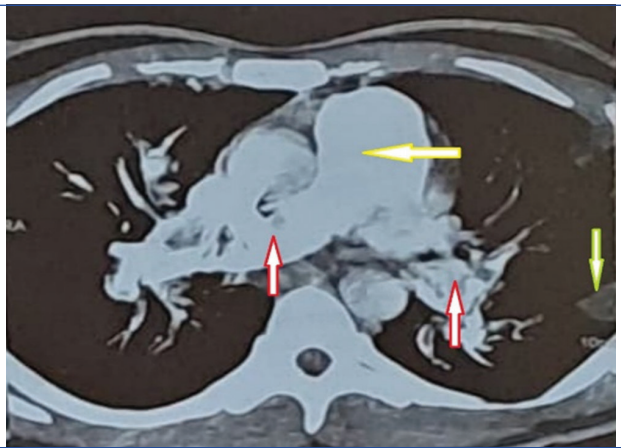
Keywords: Lupus anticoagulant, Mesenchymal cells, Pulmonary embolism

CASE REPORT

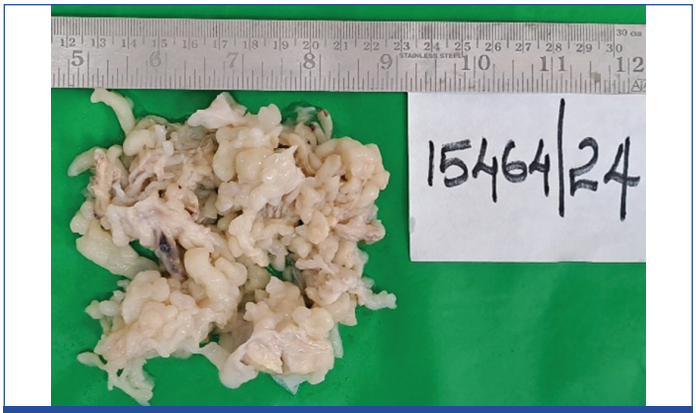
A 29-year-old male presented with complaints of right-sided chest pain, cough, and dyspnoea on exertion of two weeks duration. On examination, patient was conscious, alert, and vitals were stable. Chest radiography revealed right-sided lung infiltrates [Table/Fig-1]. ECG shows ST segment depression in II, III, and aVF. CT thorax showed extensive intraluminal filling defect within the dilated main pulmonary artery, right and left pulmonary artery, segmental branch of both lungs, suggestive of pulmonary embolism [Table/Fig-2]. Echo showed mild TR, mild PAH, and mild right ventricle dysfunction. Thrombolysis was done and failed. Further blood investigations were done to evaluate the underlying cause of pulmonary embolism, including anti-thrombin III function, protein C and protein S, Antinuclear Antigen (ANA) profile, lupus anticoagulant, Anti-neutrophil Cytoplasmic Antibody (ANCA), P ANCA, serum erythropoietin, D dimer, and the results were within normal limits. Venous Doppler of both lower limbs was taken and showed no evidence of DVT. Pulmonary endarterectomy was done as the symptoms persisted. Our histopathology department received adequately formalin-fixed multiple whitish polypoidal soft-tissue pieces attached to calcified vessel wall measuring 10×9×3 cm [Table/Fig-3] with gelatinous cut-surface. Histopathology examination showed a malignant mesenchymal neoplasm with varied cellularity arising from the vessel wall in a myxoid stroma [Table/Fig-4a]. Individual cells are plump, spindle/undifferentiated [Table/Fig-4b] with moderate eosinophilic/vacuolated cytoplasm, small hyperchromatic nuclei with moderate pleomorphism. Cells with bizarre nuclei [Table/Fig-4c] and areas of necrosis [Table/Fig-4d] are also observed. Correlating with clinical presentation, radiology, and histomorphology, a provisional diagnosis of Pulmonary Artery Intimal Sarcoma (PAIS) was considered. An immunohistochemical panel was performed to confirm the mesenchymal and intimal sarcoma phenotype and to exclude morphologically similar neoplasms, including primary pulmonary angiosarcoma, leiomyosarcoma, synovial sarcoma, and fibrosarcoma. The tumour demonstrated a high Ki-67 proliferative index (~40% in mitotically active areas [Table/Fig-5a]), diffuse vimentin positivity confirming mesenchymal differentiation, and strong nuclear positivity for MDM2 [Table/Fig-5b], supporting the diagnosis of intimal sarcoma. Negative CD31 [Table/Fig-5c]) and FLI1, excluding endothelial differentiation, as well as desmin and Smooth Muscle Actin (SMA), ruling out smooth



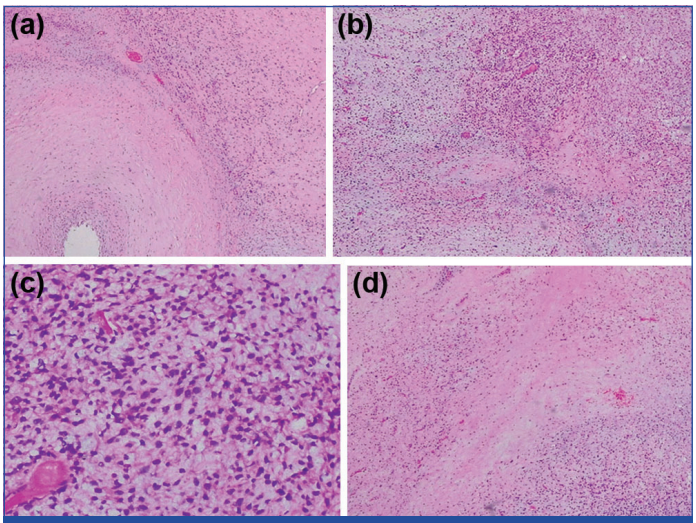
[Table/Fig-1]: Roentgenography shows right-sided lung infiltrates.



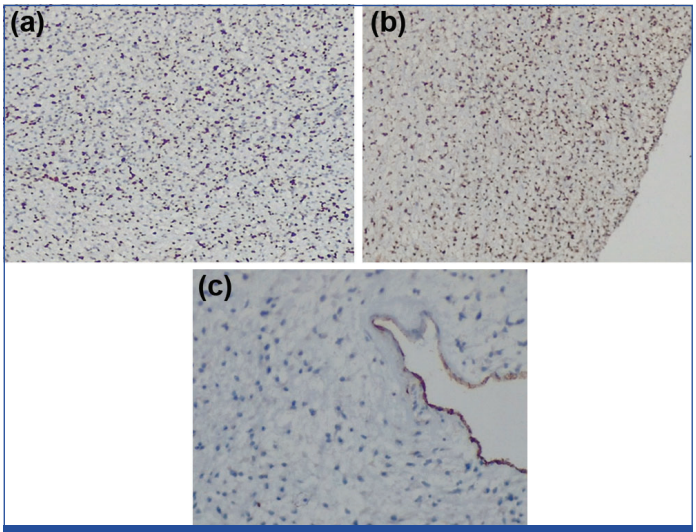
[Table/Fig-2]: CECT thorax showing dilated main pulmonary artery (Yellow arrow), left and right pulmonary arteries with multiple filling defects (Red arrows), wedge shaped pulmonary infarcts (Green arrow).



[Table/Fig-3]: Gross image.



[Table/Fig-4]: a) Malignant mesenchymal neoplasm of blood vessel (4x magnification) b) Plump, spindle/undifferentiated neoplastic cells in myxoid stroma (4x magnification). c) Neoplastic cells with bizarre nuclei 40x magnification. d) Areas of necrosis (4x magnification).



[Table/Fig-5]: a) High Ki-67 proliferative index {~40% (4x magnification)}; b) MDM2 strong nuclear positivity (4x magnification); c) CD 31 Negative (10x magnification) stains endothelial cells, tumour cells negative.

muscle differentiation. S100 negativity helped exclude nerve sheath tumours and certain differential diagnoses, including synovial sarcoma. Positive staining for Vimentin, MDM2 and high Ki-67 index in the absence of specific differentiation markers strongly supported the diagnosis of undifferentiated PAIS. Following the procedure, the patient's haemodynamics improved, and the patient is currently under follow-up.

DISCUSSION

The PAIS primary tumour of large vessels first reported in 1923 by Mandelstamm [1]. It is a highly malignant neoplasm arise from subendothelial pluripotent cells within the pulmonary artery intimal wallwith a prevalence estimated between 0.001% - 0.003% [2] (~400 cases reported in literature till 2021 [3]) having poor prognosis. It is often underestimated because of potential misdiagnosis due to its similar presentation to that of pulmonary thromboembolism [4]. Histopathological confirmation remains the gold standard. Early diagnosis is vital due to the tumour's aggressive behaviour, high metastatic potential, and high mortality rate [5].

It is estimated that the median survival for untreated PAIS to be as a low as 1.5 months (1.5-5.5 months) and10 months if surgical resection is performed [6]. The mean age of diagnosis for PAIS is variably reported, ranging in the 5th to 7th decades of life with slight female predominance [6,7]. Our patient, aged 29 years, did not fit within this demographic range, supporting the notion that PAIS also affects younger adults with no significant gender predilection.

The World Health Organisation classifies pulmonary artery sarcomas into intimal sarcoma and intramural sarcoma types Intimal sarcoma presents an intraluminal polypoid growth pattern, and usually exhibits fibroblastic or myofibroblastic differentiation. Intramural sarcoma is considered distinct from intimal sarcoma, and is classified separately according to the histological subtypes as in soft tissue sarcoma [8,9]. The most common pathological type of PAIS is undifferentiated sarcoma (34%), followed by fibrosarcoma (21%), smooth muscle sarcoma (20%), rhabdomyosarcoma (6%), mesenchymal histiocytoma (6%), intrachondral sarcoma (4%), angiosarcoma (4%), osteosarcoma (3%), and malignant fibrous histiocytoma (2%) [9,10]. Molecular studies revealed MDM2 over expression and amplification accompanied by co amplification of CDK4, PDGFRA AND TERT gene [11] as well as number losses in CDKN2A and CDKN2B [12].

Clinical manifestation is often atypical and mostly present as acute pulmonary embolism. In our case, patient presented with clinical features resembling Pulmonary Thromboembolism (PTE), including dyspnoea and chest discomfort, but maintained stable vitals. This aligns with previously reported cases where PAIS mimics PTE, often leading to initial misdiagnosis and delayed treatment [4]. Contrast-enhanced Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) can reveal an intraluminal mass with heterogeneous enhancement, distinguishing it from thromboembolic disease. Positron Emission Tomography (PET) with Fluorodeoxyglucose (FDG) may further aid in the diagnosis by demonstrating increased metabolic activity, a feature not typically seen in thrombi [13].

Grossly, it resembles a mucoid or gelatinous or fleshy polypoidal or nodular or irregular mass that fills the vascular lumen with firm fibrotic, bony, gritty or chondromyxoid regions, like descriptions by Nonomura A et al., [8]. Histopathological confirmation remains the gold standard for diagnosis. PAIS typically characterised by a malignant proliferation of spindle to pleomorphic cells originating from the intimal layer of the pulmonary artery arranged in fascicles/storiform pattern in a myxoid stroma. These tumours typically show a high degree of cellular atypia, including hyperchromatic nuclei, prominent nucleoli, and frequent mitotic figures. Necrosis and haemorrhage are common, particularly in high-grade tumours [9,10]. Immunohistochemically, PAIS often expresses vimentin, confirming mesenchymal origin. Also, MDM2 and CDK4 are expressed due to amplification of the 12q13-15 chromosomal region, which helps to differentiate PAIS from thromboembolic disease and other sarcomas as stated by Huo L et al., and Bode-Lesniewska B et al., [10,12]. Smooth Muscle Actin (SMA) and desmin may be focally positive, while endothelial markers such as CD31 and CD34 are typically negative, excluding vascular neoplasms [12,13].

Surgical resection (complete resection with negative margins) is the cornerstone of treatment and offers the best chance for prolonged survival. Incomplete resection or palliative debulking may still offer symptomatic relief and prolongation of life. Adjuvant

therapies, including radiotherapy and chemotherapy, have shown limited efficacy due to the tumour's resistance and the anatomical challenges posed by its location [14].

CONCLUSION(S)

The PAIS is a rare, aggressive tumour that poses significant diagnostic challenges, because it is mainly undifferentiated and histologically varied, even within the same host and diagnosing this sarcoma has proven difficult despite the World Health Organisation's (WHO) criteria. Due to its clinical similarity to pulmonary embolism, a high-index of suspicion is essential in patients who do not respond to anticoagulation. Timely diagnosis via histopathology the gold standard, complete surgical resection, and multimodal treatment approaches are vital for improving patient outcomes.

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