CASE REPORT

Primary proximal epithelioid sarcoma of the lung successfully treated with pneumonectomy and adjuvant chemotherapy

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SUMMARY

Primary sarcomas of the lung and proximal epithelial sarcomas (PESs) are extremely rare. Inactivation of INI1 has been found in the majority of epithelioid sarcoma (ES). We report the third known case of a primary PES of the lung along with immunohistochemical data. A 41-year-old man with HIV infection, on highly active antiretroviral therapy, presented with haemoptysis, shortness of breath and progressive weight loss for 2 months. He was eventually diagnosed with stage IIA cT2bN0M0 grade-2 primary PES of the lung. This patient underwent pneumonectomy and adjuvant chemotherapy with ifosfamide and doxorubicin. He remains in remission 36 months since diagnosis. Our case stands to help other clinicians as treatment of such rare cases is often reliant on case reports. We also posit a possible pathogenic mechanism given a history of HIV infection in this patient. The association of INI1 mutation with other atypical sarcomas in patients with HIV infection merits further evaluation.

BACKGROUND

Epithelioid sarcoma (ES) is a rare soft tissue neoplasm. A proximal-type or axial-type, variant of this undifferentiated soft tissue sarcoma was only recently described.¹ The proximal-type variant is found mostly in the pelvis, perineum, thigh and genital tract in adults.² This variant is more often deep seated, has distinct histological features, metastasises earlier and behaves more aggressively than the usual distal ES.^{1,2} Inactivation of INI1 has been found in the majority of ESs, both conventional (distal) and proximal-type variants and may be helpful in diagnosis.³ We report a case along with providing immunohistochemical data of a primary pulmonary proximal-type ES in a 41-year-old man with HIV infection. To the best of our knowledge, this is only the third reported case of primary pleuropulmonary ES.⁴

CASE PRESENTATION

A 41-year-old man with HIV infection, on highly active antiretroviral therapy (HAART), presented with a history of haemoptysis, shortness of breath and progressive weight loss over 2 months. He had been diagnosed with HIV infection 20 years prior and was compliant with his HAART regimen. His CD4 count was 192/μL, with an undetectable viral load. A CT scan of the chest showed a 4.4 cm right perihilar mass extending into the bronchus intermedius with associated

partial atelectasis of the right middle lobe. He underwent a bronchoscopy with biopsy of the endobronchial lesion, which was initially concerning for a poorly differentiated carcinoma of the lung. A subsequent full body positron emission tomography (PET) scan revealed a 6.1×4.7×4.4 cm soft tissue mass in the right middle lobe demonstrating hypermetabolic activity with a standard uptake value (SUV) of 5.1 and a suggestion of central photopenia indicating a necrotic component. There was a 0.7 cm right cervical lymph node with a SUV of 4. There were no other abnormal lesions to suggest metastatic disease. His cancer was determined to be stage IIA cT2bN0M0. Robotic video-assisted thoracoscopy was performed with a right pneumonectomy. He had a full resection of the mass with negative margins. No lymph node dissection was attempted.

INVESTIGATIONS

Histological examination (figure 1) of the tumour revealed spindle to epithelioid cells with abundant eosinophilic cytoplasm, large vesicular nuclei and prominent nucleoli. Focal rhabdoid features were evident. The neoplastic cells were arrayed mostly in solid sheets that were loosely cohesive in some areas and in other areas showed a pseudovascular pattern with multiple blood-filled spaces lacking an endothelial lining. There were occasional mitotic figures as well as rare foci of necrosis and a significant lymphoplasmacytic inflammatory infiltrate. Immunohistochemical stains (figure 2) were strongly and diffusely positive for EMA CD34 and vimentin, while negative for cytokeratin AE1/AE2, CK5/6, CAM 5.2, CD31, ERG protein, human herpesvirus-8, factor XIII-related antigen, synaptophysin, chromogranin, CD56, S-100 protein, desmin, actin, myogenin, ALK-1 CD45, CD30 and CD99. In addition, there was loss of nuclear INI-1 expression within the tumour cells. A diagnosis of grade 2 primary ES, proximal type, was established.

TREATMENT

The patient was treated with four cycles of adjuvant chemotherapy with ifosfamide plus doxorubicin, which he tolerated well.

OUTCOME AND FOLLOW-UP

Follow-up PET scans at 3 months and 10 months revealed no evidence of metastatic disease. The

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Figure 1 (A) Gross specimen of resected tumour showing necrotic centre. (B) Histopathological examination showing cellular proliferation arranged in solid sheets with occasional blood-filled spaces lacking endothelial lining (H&E, low magnification). (C) Spindle to epithelioid cells with abundant deeply eosinophilic cytoplasm, large vesicular nuclei and prominent nucleoli. (D) Focal 'rhabdoid' features are present (H&E, high magnification).

right cervical node noted in prior PET scan was not seen on the follow-up scans. The patient remains in remission 36 months since diagnosis.

DISCUSSION

Proximal ES (PES) commonly involves men in the early decades of life. Five and 10-year survival rates are between 80% and 50% respectively.⁵ While the tumour has been reported most commonly in the extremities, other locations have been reported, which include the palate, penis, perineum and the scalp.⁴ Pulmonary sarcomas account for <0.5% of primary lung tumours. To date, there has been one reported case of proximal-type ES of the pleura⁶ and one reported case of a pulmonary primary ES other than our patient.⁴

Histologically, ES can be classified into classical, spindle and mixed forms. Similarly, depending on gross location, the tumour can be classified as a proximal or axial, type—when the tumour is present proximally to the elbow. It has been observed that the PESs have worse outcomes. Proximal-type ESs are characterised histologically by a large cell type and prominent nuclei and have rhabdoid features. Histological diagnosis can be challenging due to many shared features with tumours such as extrarenal rhabdoid sarcomas, clear cell sarcoma and squamous cell carcinoma as well as granulomatous processes and inflammatory entities such as nodular fasciitis and nodular tenosynovitis. Diagnosis is now aided by immunohistochemistry. Antigens such as vimentin, cytokeratin and epithelial membrane antigen are usually positive. CD34 is positive in 50–60% of these tumours and helps in differentiating it from the extrarenal rhabdoid tumours.²

Recent evidence also points towards epigenetic risk factors such as loss of the INI1 subunit of the SWI/SNF complex

associated with chromatin remodelling. INI1 silencing events are described in a significant percentage of both proximal and distal-type ESs, including that of our patient.³ It is interesting to note, with respect to our patient's history of HIV infection, that the INI1 gene produces a host factor for the HIV virus and its integration. Studies suggest these silencing events may occur through action of OncomiRs, or microRNAs that interfere with the coding of this protein.⁷ OncomiRs have been implicated in virus-induced tumourigenesis by Epstein-Barr virus. There may be similar pathological mechanisms in the development of epithelioid tumours as well. Some studies that examined the role of P53 mutations did not find good evidence for direct involvement of either the P53 or P21 pathway in tumourigenesis.^{8 9} It is very difficult to examine the relationship between HIV infection and the incidence of extremely rare cancers. However, the association of the INI1 mutation with other atypical sarcomas such as malignant rhabdoid tumours and PES and reports of other atypical sarcomas in HIV patients, may merit further evaluation.

Owing to the rarity of the tumour, there are limited data regarding the management of ESs. Wide surgical excision remains the most common method given the high rates of local recurrence and tendency to involve underlying fascial planes.¹ Adjuvant therapy is controversial and has been documented anecdotally as being useful in high-risk tumours and advanced disease⁴; the regimens used are similar to those prevalent for soft tissue sarcomas—namely ifosfamide and doxorubicin in combination. Current consensus suggests surgical intervention along with radiotherapy and adjuvant chemotherapy. More studies are needed to solidify consensus and improve survival.

Figure 2 (A) CD34 staining showing strong and diffuse positivity. (B) Epithelial membrane antigen staining is positive. (C) Vimentin staining showing strong and diffuse positivity. (D) CD31 staining is negative in the neoplastic tissue, with positive staining in the blood vessels.

Learning points

- ▶ Primary sarcomas of the lung and proximal epithelial sarcomas (PESs) are extremely rare tumours.
- ▶ Inactivation of INI1 has been found in the majority of epithelioid sarcomas.
- ▶ Surgical resection and adjuvant chemotherapy with ifosfamide and doxorubicin may be a reasonable curative treatment option for stage III PES, depending on the site and anatomy.
- ▶ The association of INI1 mutation with other atypical sarcomas in patients with HIV infection merits further evaluation.

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