Article published online: 2020-12-31

Letter to Editor

Primary pleuropulmonary synovial sarcoma: A report of two cases and review of literature

Dear Editor,

Primary pleuropulmonary synovial sarcoma is a subset of soft tissue sarcoma. It is seen in young adults and adolescents and is a rare and aggressive tumor. Diagnosis is established by immunohistochemistry and molecular analysis. Primary modality of treatment is surgery followed by chemotherapy. Even with adequate surgical resection and postoperative treatment, recurrence of the disease and metastases are common.

A 37-year-old male nonsmoker with no background or family history of cancer or respiratory illness presented with 2 weeks history of breathlessness and nonproductive cough and a single episode of hemoptysis. Evaluation with contrast-enhanced computed tomography (CECT) chest was suggestive of a 9.1 × 10.1 × 9 cm mass lesion in the lower lobe of left lung with nonhomogeneous enhancement, abutting the pleura posteriorly. Mediastinal and vascular structures were normal. Bone scan and computed tomography (CT) abdomen were normal. Biopsy of the lesion was suggestive of synovial sarcoma. IHC: Vimentin-positive, Bcl-2-occasional tumor cells positive, CD 99, Epithelial Membrane Antigen (EMA), desmin, TTF-1, Pan CK-negative. It was planned to give him neoadjuvant chemotherapy with ifosfamide- and doxorubicin-based chemotherapy and assess response after 2-3 cycles for surgery. After two cycles of chemotherapy reevaluation CECT chest was suggestive of 5.2 × 5.0 cm hypodense lesion with large nonenhancing central area suggestive of necrosis indicative of partial response. It was planned to give him a further two more cycles of chemotherapy and reassess feasibility for surgery. After four cycles of chemotherapy surgical opinion was taken and he was advised surgery but the patient declined surgery and wanted to continue his chemotherapy in view of good response and tolerability to chemotherapy. He has completed six cycles and is under regular follow-up for the past 8 months.

A 47-year-old male nonsmoker with no family history of cancer presented with left-sided chest pain of 1 year duration. Imaging was suggestive of a large well-defined soft tissue dense mass in the left upper and midzones. He wanted to try alternative medicine and was thus lost to follow-up. As his symptoms progressively worsened biopsy of the mass was done. Histopathology was suggestive of a possibility of spindle cell neoplasm or solitary fibrous tumor of pleura. He then underwent left thoracotomy and excision of left middle lobe of lung. Intraoperative findings were suggestive of a 12 × 12 cm solitary fleshy tumor arising from the pleura and adherent to the middle lobe. Histopathology suggested pleuropulmonary synovial sarcoma with large areas of necrosis-monophasic fibrous type. IHC: Pan CK-negative, Bcl-2, vimentin, CD 99-strong positivity [Figures 1 and 2]. He was started on adjuvant chemotherapy with ifosfamide and doxorubicin. Options of consolidation with radiotherapy were discussed, but patient opted for observation. Reevaluation CECT chest after 6 cycles of chemotherapy was suggestive of CR. After a disease-free interval of 5 months, he presented with left-sided chest pain. CECT chest revealed a 4.9 × 5.4 × 4.0 cm mildly enhancing lobulated mass in the left upper lobe suggestive of recurrence. Feasibility of reexploration was considered but in view of inoperability he was put on tab pazopanib 800 mg per day. He is tolerating treatment well and is on follow-up for a duration of 17 months now. CECT chest done after 3 months of therapy with pazopanib was suggestive of stable disease. The only notable toxicity during his follow-up visits is premature graying of hair on the scalp and beard.

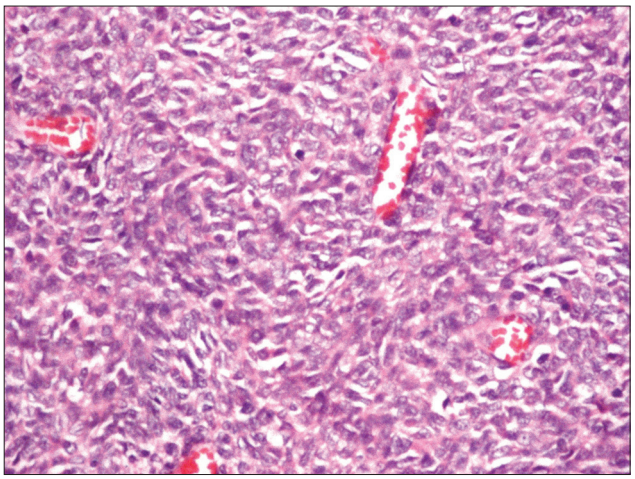

Figure 1: Section showing a cellular lesion comprised of plump spindle cells (H and E,×100)

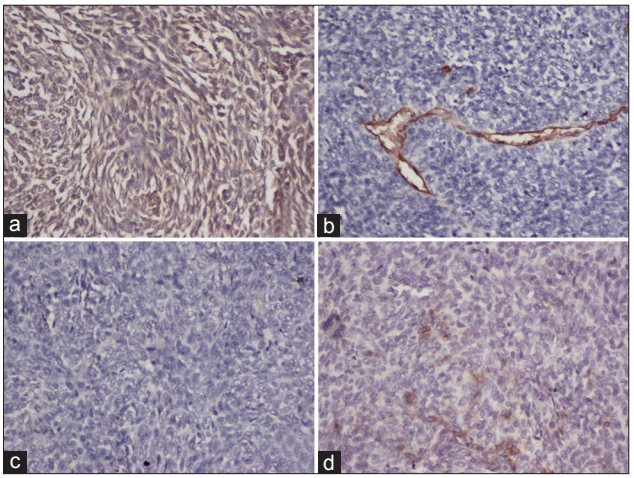

Figure 2: IHC findings, (a) Bcl2 showing diffuse positivity, (b) CD 34 negative in tumor cells with positive staining in the endothelial cells of vessels, (c) pan cytokeratin is negative in tumor cells, (d) Epithelial membrane antigen showing focal positivity in the tumor cells. (HRP-polymer based, ×100)

Synovial sarcoma accounts for 10% of all soft tissue tumors.[1,2] It presents in adolescents and young adults affecting the paraarticular locations of the extremities, neck, lung, heart, and rarely mediastinum and abdominal wall. Extremities account for 70% of the cases followed by neck and chest involvement accounting for 7% each. Pulmonary synovial sarcoma (PPSS) is a rare variant of synovial sarcoma accounting for 0.5% of all primary lung malignancies.[3] It was described as a distinct anatomic subset in 2002 by Essary *et al*.,[4] having similar pathologic features to soft tissue sarcoma. It can arise in the lung, pleura, chest wall, heart and mediastinum. A strong correlation to cigarette smoking has been postulated.[5] The median age of presentation is 25 years. There is no predilection to either sex. Both our cases were males, aged 37 and 47 years, respectively. Presentation was with pleural-based mass lesions.

Patients present clinically with chest pain (24-80%), breathlessness (8-36%), cough (8-33%), and hemoptysis (20-25%). Symptoms usually are of a few months duration. Occasionally, patients may present acutely with a rapidly enlarging tumor or pneumothorax. PPSS may be detected incidentally on a routine radiograph in at least 40% patients.[6] One of our cases presented with chest pain and the other with breathlessness and nonproductive cough. In a recent review, most of the cases of PPSS were centrally located and associated with postobstructive pneumonia.[7] Peripheral tumors were uncommon and usually slow growing and asymptomatic. Both our patients had peripheral location of tumor. Differential diagnosis includes bronchogenic carcinoma, lung metastases, mesothelioma, lymphoma, abscess, histoplasmosis, coccidiomycosis, fibro sarcoma, and leiomyosarcoma. PPSS may metastasize to bone, liver, skin, brain, and breast tissue.[8] None of our patients had metastases at presentation.

On chest X ray, it appears as a homogenous opacity in the lung, often accompanied by ipsilateral pleural effusion. It may appear as a consolidation or a complete opacification of the hemithorax or as a pleural thickening.[9,10] Rarer presentations may include pneumothorax. Significant mediastinal adenopathy is usually not seen in PPSS and argues more in favor of bronchogenic carcinoma. Other mimics could include metastases to lungs, fibro sarcoma, hemangiopericytoma, mesothelioma, and leiomyosarcoma. On CT scan, it appears as a well-defined heterogeneously enhancing mass lesion with areas of fluid indicating necrosis or hemorrhage. Both the cases in this report appeared as large masses with nonhomogenous enhancement. There was no evidence of pleural effusion. Soft tissue sarcomas arising in the chest wall display cortical bone destruction, tumor calcification, and invasion. One differentiating feature between PPSS and soft tissue sarcoma is the presence of triple sign (bright, dark, and gray) representing tumor, hemorrhage, and necrosis on magnetic resonance imaging (MRI). MRI aids in more accurate localization and is useful to know the extent of tumor invasion.[11] It was, however, not done in our cases.

Pathologic examination reveals the presence of fascicles of spindle cells with a high-mitotic rate. PPSS is believed to originate from multipotential mesenchymal cells with synovial differentiation, hence, the term synovial sarcoma. The histological subtypes of PPSS are biphasic, monophasic spindle cell, monophasic epithelial, and poorly differentiated types.[12] The monophasic variant is more commonly seen. It is composed of uniform spindle cells with elongated nuclei, basophilic cytoplasm, and indistinct cell borders. The monophasic type poses certain diagnostic difficulties due to the uniform spindle cell pattern. It may be confused with fibrosarcoma, hemangiopericytoma, leiomyosarcoma, and carcinosarcoma. These tumors are immunoreactive for cytokeratin and EMA. They also show variable positivity to S-100 (30%), CD 99 (70%), and Bcl-2 (75-100%).[13] Both cases were positive for vimentin and Bcl-2, while one case was positive for CD99. Our cases were of the monophasic fibrous variety.

Nearly all synovial sarcomas have a specific chromosomal translocation t (X; 18)(p11.2;q11.2). This results in the fusion of the SYT gene on chromosome 18 with the SSX1 or the SSX2 on chromosome X.[14] SYT-SSX1 and SYT-SSX2 are believed to function as aberrant transcription regulators. Hartel *et al*.,[15] reported that 92% patients with PPSS and mediastinal sarcoma were positive for t (X;18). SYT-SSX1 is present in majority of the biphasic tumors, while in the monophasic tumors there is an equal frequency of both translocations. There seem to be certain prognostic implications associated with the specific translocations, with SYT-SSX1 common in younger adults and having a poorer prognosis as compared to SYT-SSX2. In one study patients with SYT-SSX1 type had a poorer 5-year survival rate.[15] In another study by Mirzoyan *et al*.,[16] patients with SYT-SSX1 were younger, had similar mean tumor size and had lesser grade 3 tumors. Translocation studies were not done in our subjects.

Owing to the rarity of the tumor, there are no guidelines on the optimal treatment of PPSS. Surgery followed by radiation or chemotherapy is the current standard. Wide excision followed by radiation therapy is used in high-grade (G2–3), deep and >5 cm lesions. Radiation is given at doses of 50-60 Gy, with fractions of 1.8-2 Gy. It is also applicable in cases where R0 resections have not been achieved. Radiotherapy was not administered in our patient as he did not consent for the same.

Ifosfamide-and doxorubicin-based regimen is commonly employed with an ORR of 24%. Adjuvant chemotherapy improves the time to local recurrence with a trend toward better overall survival. In a large series of 80 patients by Spillane *et al*.,[17] chemotherapy was given in the neoadjuvant and adjuvant setting with ifosfamide and doxorubicin. The combination of these two drugs produced a 58% objective decrease in tumor size when compared to

36% when used singly. Median survival for the combination arm was 15 months.[17] In another study of 25 patients, follow-up of 18 patients confirmed that 55% had died within 7 years of diagnosis, 22% were alive with recurrent or metastatic disease, and 22% were disease-free 20 years after diagnosis. While surgery followed by ifosfamide- and doxorubicin-based chemotherapy was used in one case, the other case was treated with neoadjuvant chemotherapy due to inoperability at presentation. One case had a recurrence after 5 months and was put on oral pazopanib. Pazopanib was approved by the Food and Drug Administration in April 2012 for the treatment of soft tissue sarcoma. It is a VEGFR tyrosine kinase inhibitor which acts on all three isoforms. Pazopanib is specifically indicated in those who have failed one prior systemic therapy.

Failure to achieve a complete resection, large tumor size (>5 cm), male gender, older age (>20 years) high-grade tumor, presence of necrosis, neurovascular invasion, high mitotic rate (>10 per 10 high power fields), and SYT-SSX1 variant portend a poor prognosis.[18] The overall 5-year survival rate varies between 36% and 76%. Future therapeutic targets could include the SYT-SSX protein, EGFR, HER2/neu, and Bcl-2.[19]

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DOI: 10.4103/2278-330X.119933