

Acknowledgment

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LETTER TO THE EDITOR

Unusual presentation of syncytial variant of nodular sclerosis classical Hodgkin's lymphoma presenting as unilateral lung mass in a 15-year-old child

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A 15-year-old girl presented with complaints of low-grade fever associated with cough and weakness. This was associated with loss of weight and decreased appetite along with menstrual irregularities for 1 year. On examination the patient was conscious with stable vital signs. Air entry on the right side was reduced with swelling of the right anterior chest wall. Relevant investigations were done which showed anemia (hemoglobin: 5.2 g/dL), leucocytosis ($26.96 \times 10^3/\text{cumm}$), hyponatremia, and increased LDH (694 U/L). Coombs

test were negative. 2D echo showed trace mitral regurgitation/tricuspid regurgitation and minimal pericardial effusion. Chest X-ray was suggestive of a right sided pleural effusion. CECT chest showed a large mass arising in the right lung with mediastinal involvement. Interventional FNAC was done which showed the presence of atypical cells. Tru-cut biopsy of the right lung mass showed sheets of atypical large cells, with severe pleomorphism, multinucleate, and bizarre forms (Figure 1(A,C)). There was prominent fibrosis within the cores

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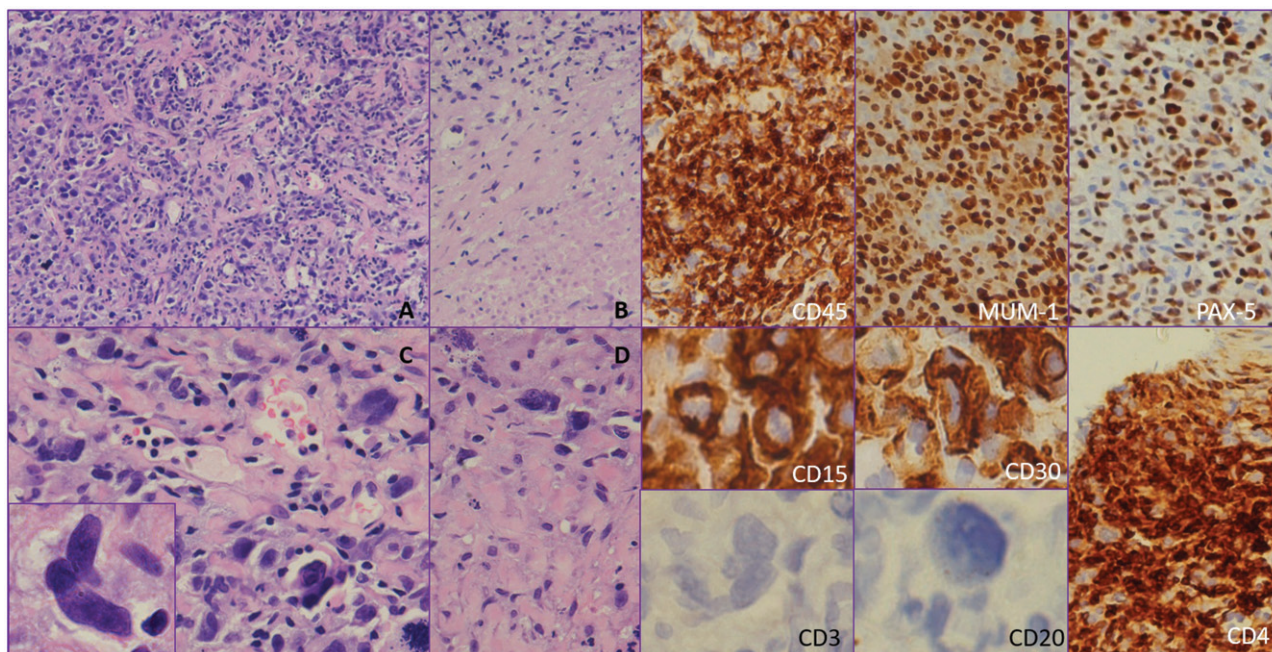


Figure 1. (A) Tru-cut biopsy shows sheets of atypical large cells, with severe pleomorphism, multinucleate and bizarre forms along with areas of fibrosis (H&E; 20×). (B) Areas of necrosis (lower right side) admixed with cellular areas (H&E, 20×). (C and D) High-power view showing the large cells with severe pleomorphism and large multinucleate forms (inset). There are prominent areas of fibrosis (D) (H&E; 40×). IHC profile of the atypical large Reed–Sternberg cells: positive for CD45 (40×), MUM-1 (40×), PAX-5 (40×), CD4 (40×), CD15 (100×), and CD30 (100×); and negative for CD20, CD3 (100×).

(Figure 1(B)). Areas of necrosis and brisk mitoses were identified (Figure 1(D)). The differentials of syncytial variant of NSCHL, anaplastic large cell lymphoma (ALCL), mediastinal B cell lymphoma, germ cell neoplasm, and poorly differentiated carcinoma were raised on morphology. A comprehensive IHC workup was done. CD45 showed variable staining of the atypical large cells; however, these were negative in majority of the cells. CD30 and CD15 were strongly positive while PAX5 and MUM-1 were moderately positive in atypical large cells. CD 20, CD3, CD138, and CD2 were non-immunoreactive in atypical large cells. The negative markers were TTF-1, CK, ALK, PLAP, synaptophysin, and desmin with patchy focal positivity in some large cells for EMA and CD4. Epstein–Barr encoding region (EBER) by *in situ* hybridization was negative. The IHC profile of the large cells (CD45-/CD20-/PAX5+/CD30+/CD15+/MUM-1+) favored syncytial variant of NSCHL, grade 2 on these core biopsies. The patchy EMA and CD4 positivity was unusual. Lack of CD20 expression helped in excluding a gray zone lymphoma. The IHC findings of negative ALK, CD3, and CD2 excluded ALCL and a T lineage NHLs. CK negativity excluded carcinoma. CK and PLAP negativity excluded germ cell origin.

Further investigations included PET-CT scan and bone marrow examination for staging. PET-CT revealed a large heterogeneously enhancing mass lesion involving right hemithorax including the lung, pleura and with extension into the ipsilateral mediastinum measuring 14.2 × 11.8 × 14 cm. There was extrathoracic extension into the anterior chest wall at the level of the 1st, 2nd, and 3rd ribs with no obvious erosion of the underlying ribs (Figure 5). Superiorly, the lesion was abutting the subclavian vessels with partial encasement of the right brachiocephalic vein with mild luminal narrowing and superior vena cava which was significantly narrowed.

The mass was abutting the ascending aorta and proximal arch of aorta, infiltrating into the AP window, precarinal, and the subcarinal region. There was mild compression of the right pulmonary artery with significant compression of the upper and middle lobe arteries and mild compression of the right lower lobe arteries. The mid and distal right superior pulmonary veins were completely encased by the mass and were not clearly appreciated on the current scan. The mass was also encasing and compressing the right main bronchus with near total obliteration of the upper lobe bronchus and its branches. There was mild extension into the prevertebral/posterior pericardial region also. The right upper lobe was completely collapsed; there was partial aeration of the right middle lobe and the right lower lobe with atelectatic changes along the margins of the above-mentioned mass. The visualized left lung appears grossly unremarkable. Enlarged FDG avid right level VB, supraclavicular, superior mediastinal, right axillary and retro pectoral and cardiophrenic nodes, largest measuring approximately 1.6 cm in the retro pectoral region. Bone marrow examination showed increased myelopoiesis with no evidence of lymphoma infiltration. The final clinical diagnosis was classical Hodgkin's lymphoma [IPS: leucocytosis, stage IV (Cotswold's modification of the Ann Arbor staging system), hypoalbuminemia, leukopenia, anemia] (high risk). The patient was started on adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy. Response assessment was monitored by PET-CT scan.

Follow up PET-CT was done twice at 3 and 6 months. The latest PET-CT done at 6 months after completion of five cycles of chemotherapy, when compared with the diagnostic report, showed a significant decrease in size (5.5 × 5.5 × 5.1 cm), extent, and metabolic activity of the mass lesion in the right

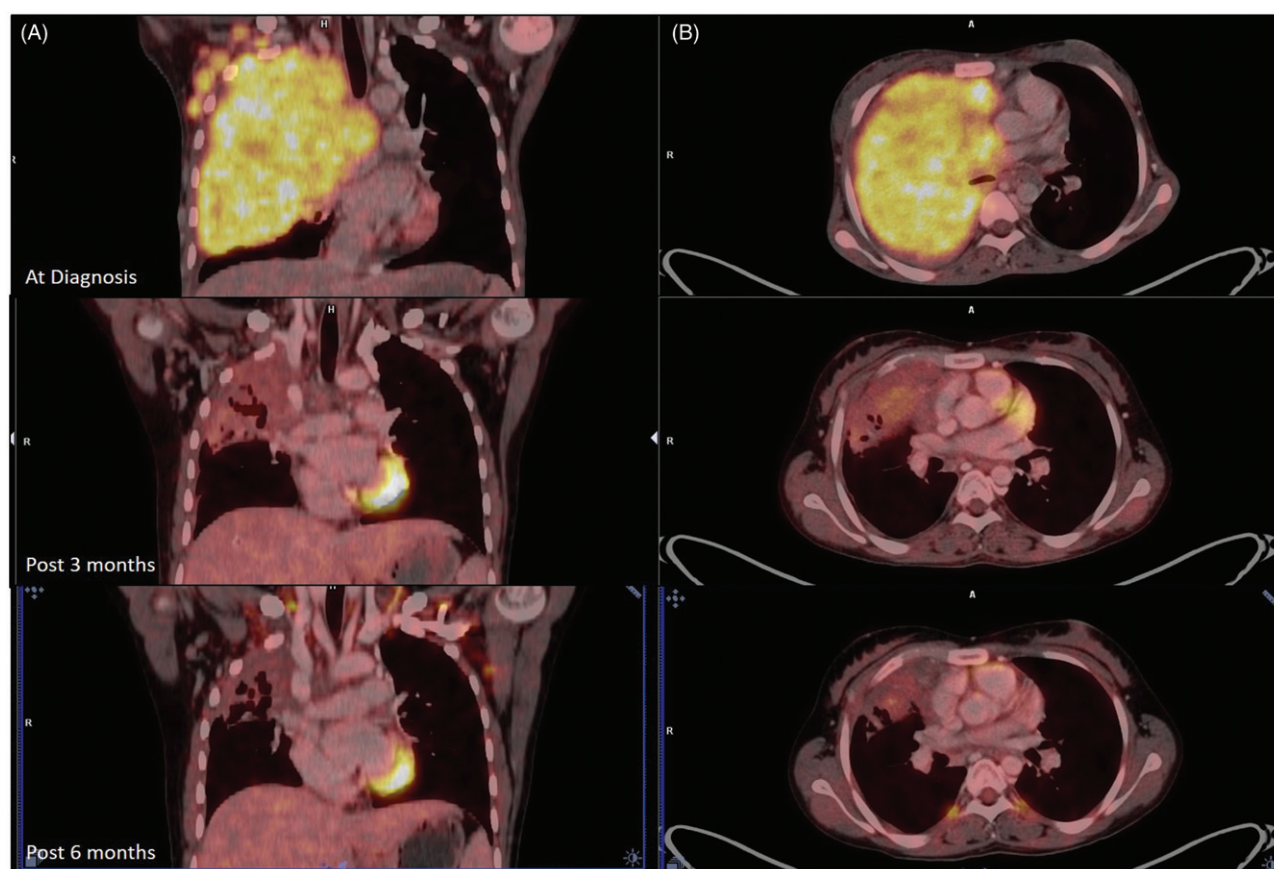


Figure 2. PET-CT scan of the patient at the time of diagnosis (top), post 3 months (middle), and post 6 months (bottom) after start of therapy. There is a large FDG avid mass, completely collapsing the right upper lobe, partial aeration of the right middle lobe and the lower lobe with atelectatic changes along the margins of the above-mentioned mass. There was subsequent reduction in the size of the mass at 3 and 6 months. The figure shows both coronal (A) and axial view (B).

hemithorax [Figure 2](#). Right axillary, right cervical level IV, and few mediastinal lymph nodes also showed significant interval decrease in size and metabolic activity. Overall, the findings suggest good response to therapy. Currently the patient has been admitted for the 6th cycle of chemotherapy. Her blood counts are normal with resolution of anemia and leucocytosis. The patient is presently not in complete remission; however, she is showing good response to treatment.

Nodular sclerosis (NS) is one of the common subtypes of classical Hodgkin's lymphoma (CHL) with a good prognosis. The syncytial variant (SV) is a less known entity, comprising ~16% of NSCHL. SV has an adverse outcome with an aggressive course, presenting as large bulky mediastinal mass, 88% of patients presenting in Stage III/IV [1]. SV presents predominantly with lymph node involvement, few rare presentations seen in terminal ileum, one of them associated with Crohn's disease [2,3]. The main challenge faced in the diagnosis is the histomorphology, which shows sheets and aggregates of large cells (Reed-Sternberg cells), which can be misdiagnosed as Non-Hodgkin's Lymphoma (NHL), melanoma, carcinoma, sarcoma, thymic carcinoma, and germ cell tumor [1].

This case posed a similar diagnostic challenge, as at the time of biopsy the mass was considered to be arising from the lung, involving the pleura and having an extrathoracic extension. Morphologically because of the sheets of atypical

large cells with areas of fibrosis, other high-grade malignancies such as carcinoma, sarcoma, thymic carcinoma, and germ cell tumors were thought. In view of the patchy CD45 positivity, hemato-lymphoid nature of the tumor was established and further IHC's (CD15, CD30, PAX5, and MUM-1) confirmed the diagnosis to be SV of NSCHL. In the present case EBER was negative, similar to all 11/43 cases of SV NSCHL reported in the study by Sethi et al. [4]. Another important question was whether the tumor was primary from the lung or has secondarily involved the lung. According to the literature, SV of NSCHL primarily arising from the lung (limited to the lung parenchyma) is extremely rare [5]. This was not the presentation with the present case, however the reported cases are few to concretely state the same. This case highlights the importance of keeping a broad differential in tumors with this morphology and employing an extensive IHC panel to arrive at a definite diagnosis.

In the study by Sethi et al., patients with SV experience had a lower than expected rate of CR with a shorter progression-free interval as compared with those with typical NS with standard therapy. This highlights the need for recognition of SV as a high-risk subgroup among the traditionally well-behaved NSCHL [4]. NSCHL has an excellent prognosis in children, when compared to adults with a worse outcome. In a recent study by Granot et al. in which there are three

pediatric patients with SV were analyzed retrospectively. All the three patients developed multiple recurrences, showed different scenarios after treatment (complete remission in one case, development of second malignancy in second, and death of the patient in the third case) with chemotherapy and bone marrow transplantation. This study showed that SV histology may be a prognostic factor for poor outcome in children diagnosed with HL [6]. To conclude, syncytial variant of NSCHL is rare in adults and few cases have been reported (only one study showing 43 cases of SV NSCHL. However, in children, the number is extremely small (literature documents only three cases till date) thus limiting the assessment of the prognosis of this disease.

Disclosure statement

No potential conflict of interest was reported by the authors.

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