

Pediatric Primary Pleural Synovial Sarcoma: A Unique Case Report with Brief Review of Literature

Abstract

Synovial sarcoma (SS) primary to the pleura is an extremely rare tumor. So far, only nine cases have been reported in pediatric patients. However, none of these patients was found to have a conglomeration of tumors. Here, we report a case of 16-year-old female with monophasic SS and synchronous occurrence of left paraspinal ganglioneuroma and a right paraovarian cystadenoma. A next-generation sequencing genetic panel revealed a novel variant of unknown significance in the MET gene. The occurrence of multiple different tumors in a young patient with a novel genetic variant in a known oncogene (MET) may suggest a possibility of a hitherto unknown cancer predisposition syndrome. We also present a brief review of primary pleural SS reported in pediatric patients.

Keywords: Children, primary pleural synovial sarcoma, synovial sarcoma

Introduction

Synovial sarcoma (SS) constitutes 8%–10% of the total soft-tissue sarcoma (STS) and is the most common form of nonrhabdomyosarcoma STS in the pediatric population. As the name suggests, it usually occurs around the joints. However, these tumors can develop at other primary sites such as the head, neck, torso, and mediastinum.^[1] Primary pleural SS is an extremely rare occurrence where SS originates in the pleura. It was first reported by Gaertner *et al.* in 1996 as a case series of 5 patients, out of which 3 were children.^[2] It has never been reported in association with other tumors. Hence, a high index of suspicion is needed to differentiate metastasis of primary pleural SS from synchronous occurrence of multiple types of tumors secondary to an undiagnosed hereditary cancer predisposition syndrome (CPS) in a young patient with a strong family history of malignancy as illustrated by our case.

Case Report

A 16-year-old previously healthy Caucasian female, a product of nonconsanguineous marriage, presented to our clinic in June 2013 with 5 years of intermittent right-sided chest pain with acute exacerbation for

3 weeks before the presentation. Medical history was unremarkable for fever, cough, shortness of breath, weight loss, night sweats, or exposure to tobacco, radiation, and environmental toxins. Family history was significant for colorectal cancer in her paternal grandmother at the age of 40 years, laryngeal cancer in the paternal grandfather in his 60s, renal cancer in her maternal grandfather in his 60s, thyroid cancer in the maternal aunt at 55 years of age, renal cancer in another maternal aunt at 64 years of age, and leukemia in the maternal great-grandmother at the age of 82 years. Multiple females in the family including mother and two maternal aunts had a history of uterine fibroids requiring hysterectomy. One of the maternal aunts also had an unknown type of skin cancer and ovarian cysts requiring bilateral salpingo-oophorectomy. The pedigree is shown in Figure 1.

On physical examination, she had decreased air entry in the right lower lung base. Laboratory workup, including complete blood count, comprehensive metabolic panel, uric acid, and lactate dehydrogenase, was within normal limits. A chest X-ray showed pleural thickening along the lateral right lower lung base. Magnetic resonance imaging (MRI) of the chest, abdomen, and

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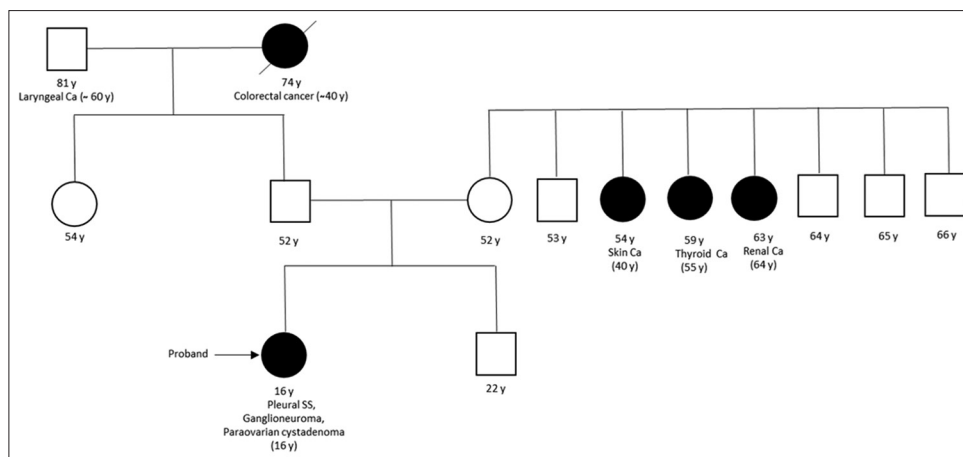


Figure 1: Pedigree chart of the patient's family showing the age of the family members. Age at diagnosis of cancer is shown in the parenthesis. Ca – Cancer

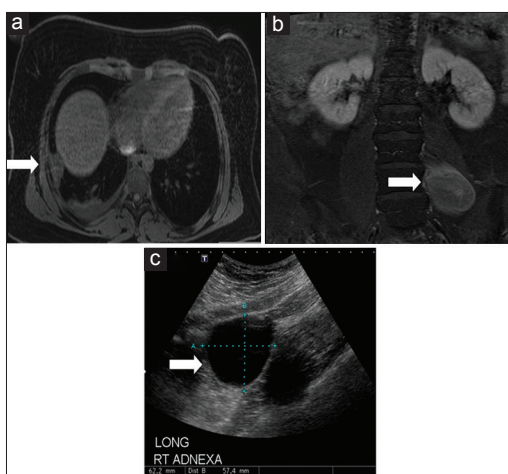


Figure 2: Radiographic images of all three tumors (white arrows) in the patient. (a) Computed tomography scan of the chest showing primary pleural synovial sarcoma. (b) Magnetic resonance imaging of the spine showing left lumbar ganglioneuroblastoma. (c) Right paraovarian cystadenoma

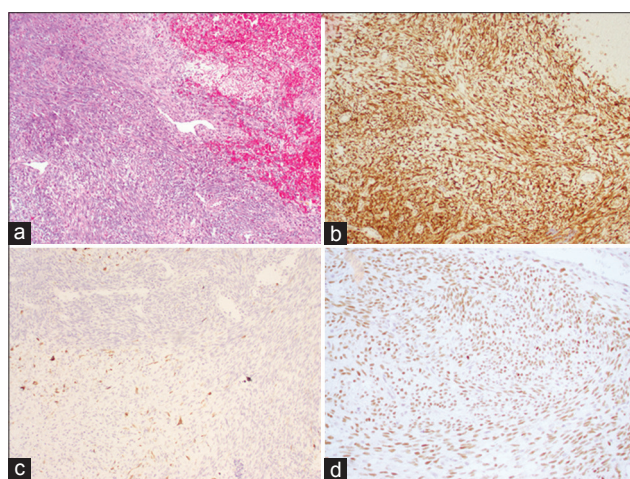


Figure 3: Histologic section showing uniform spindle cells with (a) storiform fascicular pattern and immunohistochemical expression of (b) BCL-2, (c) CK AE 1/3, and (d) TLE1

right sixth rib and a left mid-lumbar mass posterior and contiguous with the psoas muscle measuring 2.2 cm × 5 cm × 0.6 cm [Figure 2a and b]. A small right pleural effusion with adjacent right basilar atelectasis was also noted. Imaging also revealed a left paraspinal mass in the lumbar region and an ovarian cyst in the right ovary. A full-body positron emission tomography scan demonstrated a mildly hypermetabolic lesion in the lower right pleura (standardized uptake value of 2.8). A computerized tomography scan-guided needle biopsy was nondiagnostic, and hence, she underwent a right thoracotomy with an *en bloc* resection of the right pleural mass and the adjacent sixth rib. The tumor was 5.8 cm in the longest dimension with no involvement of the lung or the rib. Histologically, the mass was encapsulated and composed of uniform spindle cells arranged in sheets and fascicles with alternating areas of relative hyper- and hypocellularity [Figure 3a]. Mean mitotic count was 5/10 high-power field. Immunohistochemical studies (IHC) showed diffuse staining with TLE1, vimentin, and BCL 2 with focal EMA, CK AE1/AE3, CAM 5.2, CK7, and SMA. CD34, S100, ALK-1, p53, and HMB45 were negative [Figure 3b-d]. Ki67 was moderately increased. Cytogenetic testing by FISH was positive for SYT (18q11) translocation. These findings were diagnostic of a monophasic SS arising from the pleura. Finally, the tumor was staged and graded as Intergroup Rhabdomyosarcoma Study Group, Group III, Stage III (T2b, N0, M0), Pediatric Oncology Group Grade III (high grade), and French Federation of Cancer Centers Sarcoma Group (FNCLCC) Grade II.

A computerized tomography-guided biopsy of the left lumbar soft-tissue mass revealed it to be a ganglioneuroma. Urine vanillylmandelic acid and homovanillic acid were within normal limits. A pelvic ultrasound (US) showed a paraovarian cyst measuring approximately 4.9 cm × 4.1 cm × 3.5 cm. It was followed overtime with a pelvic US every 6 months. Following surgical resection of the pleural mass, she received therapy as

pelvis with contrast showed a 5.5 cm × 3.7 cm × 1.7 cm sharply demarcated pleural-based mass adjacent to the

per Children's Oncology Group protocol ARST0332. She was given 6 cycles of ifosfamide (9 g/m²/cycle) and doxorubicin (75 mg/m²/cycle). She received a total of 55.8 Gray (Gy) in 1.8 Gy fractions of external beam radiation therapy to the right chest wall which was started 4 weeks after the first dose of chemotherapy. She completed the last cycle of chemotherapy in January 2014. Surveillance scans with MRI chest, abdomen, and pelvis every 6 months have revealed no local or systemic signs of relapse with a stable size of the ganglioneuroma. In August 2014, she developed right lower quadrant pain. Pelvic US was concerning for interval increase in the size of the paraovarian cyst (6.2 cm × 5.7 cm × 6 cm) with possible torsion of the right ovary [Figure 2c]. She underwent right paraovarian cystectomy. Biopsy of the cyst was consistent with a serous cystadenoma. Due to the synchronous occurrence of two tumors at a young age and a significant family history of solid tumors, she underwent a genetic workup for hereditary CPS. Next-generation sequencing of an 18 gene panel (EPCAM, FH, FLON, MET, MITF, MLH1, MSH6, PMS2, PTEN, SDHA, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, and VHL) detected a novel germline missense variant of unknown significance in the MET gene NM_001127500.2(MET):c.623A>G (p.Asp208Gly). At present, the patient remains in remission 3.5 years after completion of therapy.

Discussion

The true epidemiology, clinicopathological characteristics, treatment methodology, and outcomes of primary pleural SS remain unknown due to its rarity and paucity of literature.^[1-3] Since its first description in 1997, only six additional pediatric

cases have been reported. These cases are summarized in Table 1.^[2,4-9] Evidently, the surveillance, epidemiology, and results database reporting on the incidence of SS from 1983 to 2005, and only 2 out of 213 pediatric cases (0.9%) had the involvement of lung and/or pleura.^[10] The median age of presentation of pleural SS is in the third decade of life with the most common chief complaint being chest pain. Patients may also have chronic dry cough, shortness of breath, and hemoptysis. Physical examination is mostly unremarkable but may be significant for decreased air entry in the area of lung under the lesion. Histologically, SS can be subclassified into biphasic and monophasic. Biphasic tumors have an epithelial as well as a spindle cell component with latter usually being the predominant component. Monophasic tumors are only composed of spindle cells without the epithelial component.^[11]

Accurate diagnosis of primary pleural SS may be challenging due to its relative rarity and clinicopathologic resemblance to other tumors such as malignant mesothelioma and pleural metastasis of extrapleural SS as metastatic disease portends a much worse prognosis. In addition, malignant solitary fibrous tumor, leiomyosarcoma, liposarcoma, mesenchymal chondrosarcoma, peripheral nerve sheath tumor, and malignant vascular tumors are other high-grade and aggressive sarcomas of the pleura.^[12] Histopathology along with its unique IHC staining pattern (TLE1 and Bcl-2 positivity) and cytogenetic features, *t*(X; 18)(p11.2; q11.2), is pivotal to the definitive diagnosis of this rare clinical entity.^[12,13]

Due to the very small number of cases, the optimal treatment of localized primary pleural SS remains unclear.

Table 1: Summary of pediatric cases of primary pleural synovial sarcoma

Case number	Author, year (reference)	Age (years)/sex	Histologic subtype	Therapy	Follow-up (at the time of Published)
1	Gaertner <i>et al.</i> , 1996 ^[2]	17/female	Biphasic	Complete resection with lobectomy + I + D and RT	Died after 12 months
2	Gaertner <i>et al.</i> , 1996 ^[2]	17/female	Biphasic	Complete resection + I + D and RT	Died after 18 months
3	Gaertner <i>et al.</i> , 1996 ^[2]	9/male	Biphasic	Complete resection + I + D and RT	Alive with disease at 8 years
4	Jawahar <i>et al.</i> , 1997 ^[4]	18/female	Biphasic	Complete resection + I + D and RT	Alive with disease at 16 months
5	Ng <i>et al.</i> , 2003 ^[5]	15/male	Monophasic	Complete resection + I + D and RT	Alive with disease at 16 months
6	Nishio <i>et al.</i> , 2005 ^[6]	18/male	Monophasic	Complete resection + I + D and RT	Alive with disease at 2 years
7	Bégueret <i>et al.</i> , 2005 ^[7]	16/female	NR	Complete resection + I + D and RT	Alive with disease at 36 months
8	Taylor <i>et al.</i> , 2008 ^[8]	16/male	Monophasic	Complete resection + I + D and RT	Died after 6 months
9	Won <i>et al.</i> , 2016 ^[9]	17/female	Monophasic	Complete resection + VDC + IE and RT	Died after 37 months

C – Cyclophosphamide; D – Doxorubicin; E – Etoposide; F – Female; I – Ifosfamide; M – Male; NR – Not reported; RT – Radiation therapy; V – Vincristine

According to the published literature, these tumors are treated as a localized SS of any other site.^[14] Most of the reports on primary pleural SS in pediatric patients use a combination of wide surgical resection (1–2 cm margin) and radiation therapy (55.4 Gy with boost, if necessary) with adjuvant chemotherapy consisting of anthracyclines and alkylating agent (6 cycles of ifosfamide and doxorubicin) [Table 1].^[2,4-9] While addition of radiation therapy has been shown to increase the overall survival in large-scale pediatric studies, the present chemotherapy anthracycline-based regimen improves response rate without any survival benefit.^[15,16] Based on the limited literature, the rate of recurrence seems to be higher for pleural synovial SS as compared to other SS.^[2,4-9] Furthermore, management and prognosis may differ markedly for localized versus metastatic neoplasms, especially in case of SS. Therefore, detection of synchronous/metachronous tumors on metastatic workup at the time of diagnosis should always raise an alarm for a metastatic disease of chest wall rather than a primary neoplasm. Hence, the current data on primary pleural SS suggests a dire need for collaborative, multi-institutional, histology-driven clinical studies to define the true etiology, prognostic factors, and more effective therapies for this rare disease.

Finally, with reference to the above-mentioned literature about primary pleural SS, our case is unique due to the following reasons. First, to the best of our knowledge, pleural SS has never been described in an association with synchronous or metachronous occurrence of other tumors as seen in our patient. Moreover, the occurrence of three tumors in a teenager who has a significant family history of solid tumors alerted us to investigate further for a potential CPS. While the types of tumors that our patient had were not suggestive of a previously defined CPS and testing of multiple genes associated with cancer predisposition did not detect any disease-causing mutations, it is worthwhile to note that a variant of uncertain significance was found in the MET gene as reported in the ClinVar database.^[17] Unfortunately, due to unavailability of tissue sample and insurance approval, we could not investigate the causal relationship between this genetic variant and occurrence of multiple tumors. Activating mutations in MET gene are also associated with hereditary papillary renal carcinoma. The patient herself has not had renal involvement, but there is a family history of renal cancer. Finally, our patient has shown excellent durable response as compared to the previously reported cases of SS. While most of the patients either had relapsed or succumbed to disease relapse after 3 years, our patient remains in remission 4 years after diagnosis.^[2,4-9]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The

patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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