Multiple axillary-infraclavicular lymph node metastasis from malignant rhabdoid tumor of unknown primary site

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Malignant rhabdoid tumors (MRT) mostly originate from the kidney and central nervous system. However, they may also originate from retroperitoneal and paravertebral regions, mediastinum, liver, chest wall, extremity, and neck, as well as from the soft tissues. The most important method in the differential diagnosis is the analysis of cytogenetic alterations in the INI1 gene. A six-month-old girl presented with multiple conglomerated lymphadenopathies located in the anterior axillary line. MRT diagnosis was confirmed by loss of INI1 expression in the tumor tissue. This is the first case in the literature with unknown primary focus diagnosed from lymph node metastasis.

Key words: disseminated malignant rhabdoid tumor, child, unknown site, INI1 expression, immunohistochemistry.

Malignant rhabdoid tumor (MRT), first defined as a distinctive neoplasm of the kidney, is characterized by a more aggressive behavior and shorter survival as compared to the other tumors of the kidney[1-3]. Later, MRT was also shown to originate from the central nervous system[4, 5]. It may also originate from retroperitoneal and paravertebral regions, mediastinum, liver, chest wall, extremity, and neck, as well as from the soft tissues[1-3,6-11]. There have been few reported cases of congenital disseminated MRT seemingly present as a distinct entity[2].

The most important method in the differential diagnosis is the analysis of cytogenetic alterations in the *INI1* gene[12,13]. The *INI1* gene is located on chromosome 22q11.2. The protein encoded by the gene is a member of the human Switch/Sucrose Non-Fermentable (hSWI/SNF) chromatin-remodeling complex; it plays a role in regulating the transcription and functions as tumor suppressor[2,12-14]. Loss of INI1 protein expression can be shown immunohistochemically. Loss of INI1 expression is quite specific for MRT, whereas it is a rare condition for the other tumors[2, 12-14].

To the best of our knowledge, no case presented with metastatic lymphadenopathy with unknown primary focus has been reported previously.

Case Report

A six-month-old girl had been investigated for complaints of a mass located in the anterior axillary line two months before in a peripheral hospital. Multiple lymphadenopathies and bilateral pleural effusion had been detected in this hospital. We learned that bilateral pleural effusion was treated with antibiotics, steroids and with drainage of the effusion on the left side. The patient was referred to us upon the histopathological diagnosis of malignant chordoma. On physical examination, multiple conglomerated lymph nodes in a diameter of 4x3 cm were palpated at the left anterior axillary line. Left axillary ultrasonography (USG) showed conglomerated lymph nodes with a diameter of 24x46 mm. Thoracic computed tomography (CT) showed 24x40 mm conglomerated multiple lymph nodes with diffuse contrast enhancement at the left anterior axillary line. Abdominal CT and USG were normal. Cranial magnetic resonance imaging (MRI) was normal. An excisional lymph node biopsy was performed. Tuberculin skin test was negative. Hepatic and renal function tests were normal. Laboratory findings were as follows: hemoglobin: 12.4 g/dl, white blood cell count: 5000/mm^3, platelet count: 783000/

mm^3, immunoglobulin (Ig)A: 9.56 (17-69 mg/dl), IgM: 472 mg/dl (32-203), and IgG: 404 mg/dl (304-1231). Serum alpha fetoprotein level and urinary vanillylmandelic acid were normal. There was no blastic infiltration or rosette formation in the bone marrow. Serological tests for toxoplasmosis, rubella, infectious mononucleosis, and cytomegalovirus infection were all negative. CD4/CD8 ratio was 0.65. Nitroblue-tetrazolium test for chronic granulomatous disease was normal.

The histopathological examination of the first and second lymph node specimens showed sinusoidal infiltration of large, polygonal, pleomorphic cells with large, rounded, vesicular nuclei, and prominent nucleoli. The cells presented rhabdoid features with eccentric nuclei and inclusion-like nucleoli (Fig. 1a). The differential diagnosis was based on tumors presenting rhabdoid features like MRT, malignant melanoma, malignant mesothelioma, proximal type epithelioid sarcoma, and angiosarcoma. The immunohistochemistry showed total loss of INI-1 expression (Fig. 1b) with focal CD34 positivity and limited cytokeratin positivity. Immunohistochemical staining for S100, vimentin, EMA, calretinin, and WT1 was positive, while CD1a, CD31, desmin, myogenin, CD45, CD30, MPO, CD68, HMB45, HBME1, Fli1, and FVIII were completely negative. Morphological and immunohistochemical findings were consistent with a disseminated MRT.

Bilateral pleural effusion predominantly on the left side and rapid progression of masses developed during the investigations. The patient was placed on a course of chemotherapy including vincristine, 0.05 mg/kg/day, maximum dose, 2 mg/day, on day 1; cisplatin, 3 mg/kg/day, 3 days; adriamycin, 1 mg/kg/day, 2 days; and cyclophosphamide, 5 mg/kg/day, 5 days. After the second cycle of chemotherapy, bilateral pleural effusion appeared. T2-weighted chest MRI revealed multiple conglomerated hypointense masses invading to adjacent structures including the chest wall, neck, pleura, and mediastinum (Fig. 2). Cytopathology of pleural effusion was consistent with the involvement of MRT. Diffuse ascites developed in addition to rapid progression of the masses within days. The patient died of progressive disease in the third month of the diagnosis.

Discussion

Malignant rhabdoid tumor (MRT) is a very aggressive tumor, first described in the kidney, but later shown to possibly originate from various regions, including the central nervous system, retroperitoneum, paravertebral region, mediastinum, liver, chest wall, and neck[1-3,6-10,12,15-18]. It may present as disseminated disease likely to cause distortion of the normal anatomic structures[2]. White et al.[2] reported nine infants, only six of whom presented a dominant mass, which was localized other than in the kidney and central nervous system.

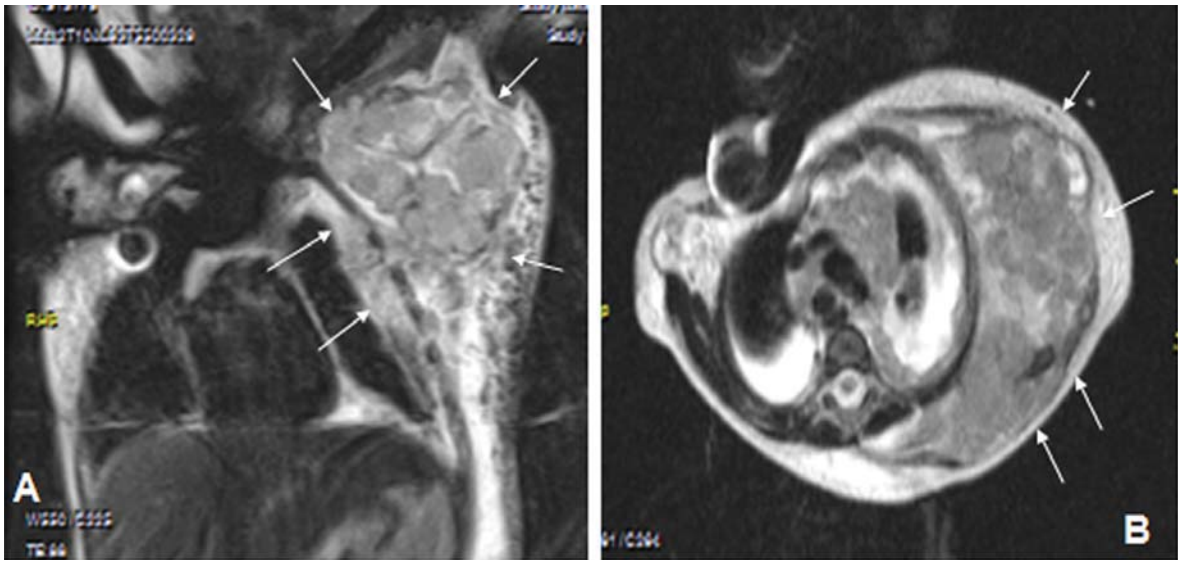

Fig. 1. Coronal **(A)** and axial **(B)** T2-weighted images showing multiple conglomerated hypointense masses infiltrating the chest wall, pleura and mediastinum.

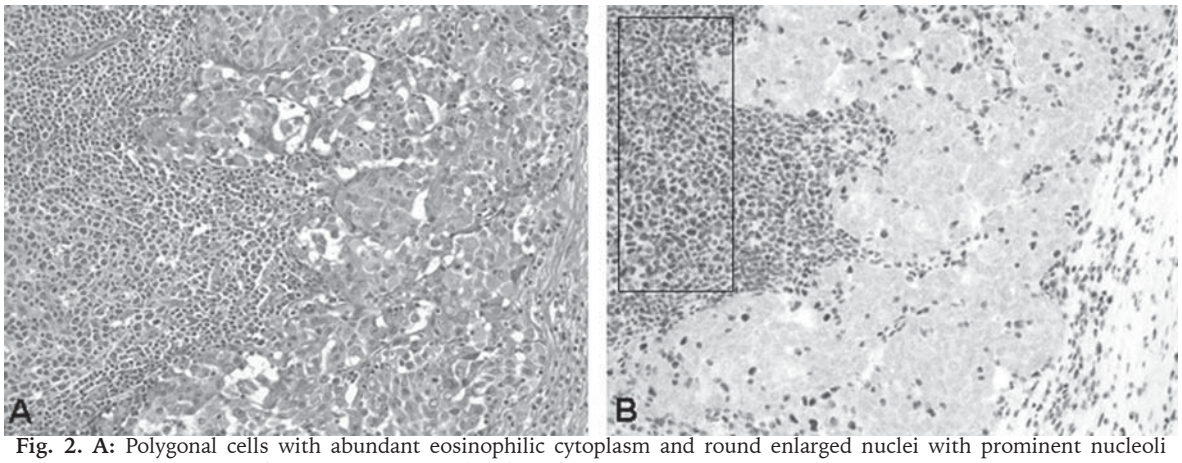

Fig. 2. A: Polygonal cells with abundant eosinophilic cytoplasm and round enlarged nuclei with prominent nucleoli infiltrating the sinusoids (hematoxylin&eosin [HE]x100). **B:** The tumor cells show complete loss of INI-1 expression (compare with the INI-1-positive lymphoid cells at the left corner) (x100) (courtesy of Dr. Andrew Folpe).

Diagnosis made from a metastatic lymph node with unknown primary origin, as in the present case, is one of the atypical clinical presentations. To our knowledge, no similar case has been reported previously in the literature.

Histopathological examination revealed that the tumor consisted of rhabdoid cells. The tumor showed polyphenotypic features with diffuse vimentin, focal EMA and cytokeratin positivity on immunohistochemical examination. The diagnosis was confirmed by showing loss of INI1 expression in the tissue, which was reported to be specific for MRT[1,2]. The *INI1* gene is located on chromosome 22q11.2[1]. Protein product of the gene is a member of the hSWI/SNF/INI1 chromatin-remodeling complex and plays a role in regulation of transcription[1,12,19]. The gene can be inactivated by germ-line or somatic mutations; however, how this mutation leads to rhabdoid tumor remains unclear[1,19].

Although loss of INI1 expression immunohistochemically has been accepted as a specific marker for MRT[1-2,4,7,15], it has also been reported in choroid plexus carcinomas, primitive neuroectodermal tumors of the central nervous system (cPNETs), medulloblastomas, glioblastoma, rhabdomyosarcoma, synovial sarcoma, renal medullary carcinoma, and epithelioid sarcoma[9,18]. Therefore, clinical characteristics of the patient, histopathological features, and other immunohistochemical markers should be taken into consideration while making the MRT diagnosis.

Another feature of our patient was the decreased serum IgA levels and T helper cells observed in the examinations, which were performed because of the presence of conglomerated lymph nodes at admission. We suspected transient partial IgA deficiency since the patient was under the age of four years and IgA level was over 7 mg/dl. On the other hand, the relatively elevated IgM level, steroid-responsive pleural effusion, and low number of T helper cells brought the possibility of immune dysregulation. No immune system change has been reported in the literature.

The prognosis of patients with MRT is very poor, and median survival has been reported as 16.75 months and two-year overall survival as 70% in tumors originated from the central nervous system[12]. Five-year overall survival was 26% in cases with tumors originating from the kidneys[20]. On the other hand, Sajedi et al.[10] reported that 18 of 21 extrarenal non-central nervous system MRT cases died.

To our knowledge, the present case is the first patient to present with involvement of a lymph node with unknown primary origin, and diagnosed definitively as rhabdoid tumor by demonstrating loss of INI1 expression. Immune deficiency, lymphoma, autoimmune disease, and metastases of other solid tumors were also investigated because of lymph node involvement. Investigating loss of INI1 expression may provide prompt diagnosis in all cases with aggressive progression, in which the diagnosis is difficult.

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