Isolated Myeloid Sarcoma: A Unique Porta Hepatis Location in a 2-Year-Old Child

Adil Abdelhamed Abbas1,2, Hatim Qasim Almaghraby1,3

Abstract:
Myeloid sarcoma (MS) or chloroma represents extramedullary accumulation of immature myeloid cells. In the World Health Organization classifications, these tumors are called granulocytic sarcomas. MS may occur concomitantly or precede the development of myeloid tumors such as acute myeloblastic leukemia (AML) by several weeks to months. Occasionally, MS represents extramedullary blast transformation of chronic myeloid leukemia and other chronic myeloproliferative neoplasms and myelodysplastic syndromes or indicates relapse in previously treated patients. Immunohistochemistry represents the gold standard of histopathological diagnosis, given the similarity of the MS medium to large-size tumor cells to many other malignant cell infiltrates making them hard to identify. Diagnosis is often difficult to reach and is missed in up to 50% of the isolated MS lesions, especially when immunohistochemistry is not properly used. MS can affect variety of body tissue organs such as the skin, bone, gastrointestinal tract, mucosal tissue, and the central nervous system. Isolated MS of the biliary system is rare. We report a 2-year-old boy with isolated MS affecting the porta hepatis (PH) who responded well to AML-type chemotherapy. Few cases of MS were reported in pediatric patients affecting the liver and biliary system. The development of isolated MS in the PH is extremely rare and has not been previously reported in the literature. To our knowledge, this is the first child to be reported with sole involvement of such location.

Keywords:
Granulocytic sarcoma, isolated myeloid sarcoma, myeloid sarcoma, porta hepatitis

Introduction
Myeloid sarcoma (MS) or chloroma is a rare extramedullary hematopoietic malignant aggregation of myeloid blasts. In the World Health Organization classifications, these tumors are called MS rather than granulocytic sarcoma (GS). MS is primarily located in extramedullary sites such as the skin, bone, lymph nodes, central nervous system, and gastrointestinal tract. The most common location for the lesions is the abdominal cavity mainly affecting the stomach, small intestine, pancreas, colon, rectum, and anal canal.[1-7]

MS is often diagnosed together with coexisting acute myeloblastic leukemia (AML) or another myeloid neoplasm. MS can also occur in isolation as a primary, nonleukemic tumor. MS might represent the first manifestation of AML, predating it by months or years or be the first manifestation of relapse even without bone marrow (BM) involvement.[8,9] Radiologic tests such as ultrasound, computerized tomography (CT), and magnetic resonance imaging scans help locating the soft-tissue mass, but are not diagnostic. Therefore, tissue biopsy and histopathological examination are essential to establish the correct diagnosis. Histological diagnosis is generally complex and requires vigilance and understanding that some AML immunohistochemical markers may be negative.[10] Isolated MS is very rare with an incidence of <2 in 1,000,000. MS affects all age groups and has been described in patients aged 2–81 years.
Isolated MS of the biliary system is rare. We report a 2-year-old patient with isolated MS of the porta hepatis (PH). We extensively reviewed the literature and found no reported similar pediatric patient. Our patient is the first to be reported with such rare presentation.

Case Report

A previously well 2-year-old child developed vague abdominal pain and progressive yellow discoloration of the sclera together with dark urine and pale stools over a period of 4 weeks. He was seen at a local hospital where ultrasound examination showed liver tumor and the diagnosis of hepatoblastoma (HB) was suspected. When arrived in our hospital, the child appeared well but was deeply jaundiced. He had no pallor, palpable lymph nodes, skin or mucosal bleedings, and had no visible dysmorphic features. There was no liver or the spleen enlargement. A vague, medium size, deeply seated, firm, and nontender mass was felt to the right of the center of his abdomen. CT scan examination showed a soft-tissue PH mass 5 cm × 4.5 cm × 3.7 cm compressing the vascular structures and the common bile duct. The liver was mildly enlarged with evidence of vascular engorgement and dilated intrahepatic bile ductules [Figure 1a and b]. There were no other enlarged lymph nodes or masses in the abdomen or chest. The full blood count showed hemoglobin of 12 × 10^9/L, lymphocytes 5 × 10^9/L, and monocytes 0.49 × 10^9/L, neutrophils 5.6 × 10^9/L, eosinophils 0.49 × 10^9/L, lymphocytes 5 × 10^9/L, and a platelet count of 355 × 10^9/L. The peripheral blood smear showed no abnormal cells. The serum bilirubin was 170 mmol/L (n < 17) and the direct bilirubin 145 mmol/L (n < 17). The serum lactate dehydrogenase was 266 IU/L (n < 245). The liver enzymes were mildly elevated; aspartate aminotransferase 76 IU/L (n = 21–44), alanine aminotransferase 74 IU/L (n = 7–44), Gamma-glutamyl transferase (GGT) 97 IU/L (n = 11–86), and alkaline phosphatase 657 IU/L (n = 156–369). The renal function was normal. The serum alfa fetoprotein level was <2 ng/dl (n < 12) and the serum beta human chorionic gonadotropin was <1.2 ng/dl (n < 1.2).

An open true cut mass biopsy of the PH mass was obtained. Complete surgical resection was not possible as the mass seemed to have been heavily attached to the PH structures. Histopathology revealed MS [Figure 2a-d]. Tumor cells were positive for myeloperoxidase, lysozymes, CD34, CD43, and CD68. Ki67 showed high proliferative index. The cells were negative for CD99, CD45, CD3, CD5, CD20, CD30, CD34, NSE, Desmin, SMA, EMA, TdT, ALK, CD56, and CD117 (granulocytic myeloperoxidase GS type). BM aspiration and biopsy revealed no evidence of leukemia. Cerebrospinal fluid examination as well showed no evidence of malignant infiltration.

The child was diagnosed with isolated MS of the PH. There was no evidence of disease elsewhere. Cytogenic and molecular examination of the PH tissue biopsy specimen revealed no adverse cytogenetic or molecular features. Therefore, we stratified him to the standard risk arm of the locally developed CAML09 protocol for treatment of AML. Induction chemotherapy (CTR) courses consisted of cytosine arabinoside, daunorubicin, and etoposide (ADE). Clinical and radiological response to the first two induction ADE cycles was very good with clearance of jaundice and near total resolution of the PH soft tissue mass [Figure 3]. He was then...
**Discussion**

MS or chloroma is a rare extramedullary hematopoietic malignant aggregation of myeloid blasts. MS are composed of diffuse tissue infiltrate made up by medium-to-large myeloid cells. These cells are sometimes difficult to identify precisely as they have great similarity to some other large size tumor cells.\(^{[10,12,13]}\) Tissue imprints following biopsy may be useful to give the first clues to the diagnosis. Histological diagnosis therefore is generally complex, and requires a high index of suspicion and understanding that some AML immunohistochemical markers may be negative.\(^{[10]}\) Immunohistochemistry is the key in making the definite diagnosis. Immune cellular markers may help differentiating the four types of GS; granulocytic myeloperoxidase (MPO+, CD 68+ [KPI±, PGM1−] lysozyme+, CD 34±), monoblastic (MPO−, CD 68+, [KPI+, PGM1+] lysozyme+, CD 34), myelomonoblastic (MPO−, CD 68+, [KPI+, PGM1+] lysozyme+, CD 34−), and the megakaryoblastic type (positivity for factor VIII, CD 61, CD 31). Immunohistochemistry may sometimes demonstrate expression of CD 43, CD 7, CD 79a (particularly the monoblastic variant with t (8; 21). However, demonstration of CD56 is very rare.\(^{[14]}\) In one case series, up to 75% of cases were misdiagnosed as large cell lymphoma. Differentiating MS from lymphoma is sometimes challenging as GS will often express some aberrant B or T-cell makers. Recently, the demonstration of CD 99 and CD 117 positivity, which can now be performed on paraffin sections, may be useful to identify granulocytic blasts.\(^{[15,16]}\)

Isolated MS of the biliary system is rare. Our patient was diagnosed with isolated MS of the PH at 2 years of age. We extensively reviewed the literature and found no reported similar pediatric patient. Few years ago, we had a patient who presented with short history of severe progressive jaundice and itchiness. That patient was 3 years old when he was diagnosed with MS overlying the PH and partially invading the liver and the pancreas. Tissue biopsy confirmed MS. His BM, however, was extensively involved with myelomonoblasts, confirming the diagnosis of AML. Just before starting CTR, the patient was given 2 fractions of radiotherapy (RT) to the PH (3 Gy) with resultant rapid relive of common bile duct obstruction and resolution of the jaundice and itchiness. He completed his treatment for myelomonocytic AML nearly 15 years ago but lost follow up shortly after his treatment completion. When our current patient initially presented to the hospital, and based on our previous experience with that patient, we considered the diagnosis of MS among the other possible conditions. We believe that mentioning our previous patient here was truly relevant as he was the one to always remained us to think of the diagnosis. Unfortunately, and for reasons concerning the availability of his diagnostic material, we were not able to report the case to the literature. Compared to that patient, our current patient had a different unique clinical presentation, as he was diagnosed with isolated MS of the PH. BM examination revealed no abnormal cells. Other conditions such as lymphoma, germ cell tumors, HB, and hepatocellular carcinomas were excluded using radiological tests, tumor markers, and histopathological examination, making this presentation unique to this child.

MSs are generally treated with CTR only in a similar way to AML (other than acute promyelocytic leukemia). Increased survival is noted for some adult patients undergoing allogeneic BM transplantation (BMT).\(^{[17]}\) The prognosis and the treatment outcomes are similar between the two entities.\(^{[18]}\) However, application of the risk stratification criteria for AML to guide treatment is often difficult especially in isolated MS lesions. Tissue cytogenetic panel and molecular studies are very helpful despite the poor yield; however, they are not always available and/or successful. Radiological response might be of help especially when other criteria are absent.

The use of RT to treat MS is not common as myeloid cells are often very sensitive to CTR. However, RT is sometimes preferred by some clinicians to obtain quicker sustained response.\(^{[19]}\) RT could be used together with CTR or Allogenic BMT as part of combined modality therapy or reserved for palliation of symptomatic or rapidly progressive lesions. RT may also be considered a consolidative treatment for isolated MS without BM
involvement, or during BM remission after systemic CTR. In general, data on treatment outcome from RT in MS is limited and most previous studies are case series reports.[17,19,20]

We treated our patient using the locally developed AML15 protocol (MRC-AML15 based) for treatment of AML. We stratified him to the standard risk arm of the protocol based on his cytogenetic examination findings and response following the first two ADE (cytosin ADE) cycles of CTR. CT scan evaluation following the first two induction cycles of CTR showed nearly complete resolution of the MS lesion.

To our knowledge, our patient is the first child with isolated MS of the PH to be reported. On immune-histopathologic examination, our patient had myeloperoxidases, lysozyme, CD68, and CD43 positivity, confirming the diagnosis of granulocytic myeloperoxidase MS subtype. Histologic subtype, however, has no known influence on the prognosis as all subtypes carry more or less the same treatment outcome.[10,14]

Although rare, the diagnosis MS should be suspected in any patient presenting with soft tissue mass involving the PH. Proper histopathological examination and immunohistochemical panel should be performed to reach the correct diagnosis and avoid delay in therapy.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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