

Extramedullary Myeloidsarcoma in Children Presenting with Pancreatic Tumor

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Abstract

Background: Myeloidsarcoma (MS) is a tumor composed of granulocytic precursor cells occurring in an extramedullary location. MS are rare neoplasms whose knowledge is largely based on case reports. MS is often initially misdiagnosed, the most common alternative diagnoses being lymphoma, undifferentiated cancer, malignant melanoma, extramedullary hematopoiesis and inflammation. Immunohistochemistry and immunophenotyping are crucial for the accurate diagnosis of MS.

Aim: The aim of this study is to introduce a boy with a very rare clinical case of MS in the diagnosis of myelodysplastic syndrome.

Case Report: A 9 year old boy with extramedullary MS has been treated in Pediatric Oncology Department, K hospital from May, 2016 to August, 2016.

Method: Retrospectively describe a clinical case.

Result: The patient is described similar to some other cases in literature. He was treated with an Acute Myeloicytic Leukemia conventional chemotherapeutic protocol and discharged.

Conclusion: The case is rare in clinical practice. The exact diagnosis was made by immunohistochemistry and immunophenotyping. Treatment with systemic chemotherapy was associated with his primary favorable survival outcome.

BACKGROUND

A myeloid sarcoma (chloroma, granulocytic sarcoma, extramedullary myeloid tumor), is a solid tumor composed of immature white blood cells called myeloblasts [1], [2]. A chloroma is an extramedullary manifestation of acute myeloid leukemia; in other words, it is a solid collection of leukemic cells occurring outside of the bone marrow.

The condition now known as chloroma was first described by the British physician A. Burns in 1811, although the term *chloroma* did not appear until 1853 [3], [4]. This name is derived from the Greek word *chloros* (green), as these tumors often have a green tint due to the presence of myeloperoxidase. The link between chloroma and acute leukemia was first recognized in 1902 by

Dock and Warthin [5]. However, because up to 30% of these tumors can be white, gray, or brown rather than green, the more correct term *granulocytic sarcoma* was proposed by Rappaport in 1967 and has since become virtually synonymous with the term *chloroma* [6]. Currently, any extramedullary manifestation of acute myeloid leukemia can be termed a granulocytic sarcoma or chloroma.

Granulocytic sarcoma may occur in patients with a diagnosis of myelodysplastic syndrome (MDS) or myeloproliferative syndromes (MPS) (e.g. chronic myelogenous leukemia (CML), polycythemia vera, essential thrombocytosis, or myelofibrosis) [7]. This rare manifestation is often misdiagnosed as non Hodgkin's lymphoma or other malignant diseases. Immunohistochemistry and immunophenotyping are

crucial for the accurate diagnosis of MS. In adults with AML, the incidence rate of MS is about 2–5%. In children, it varies in the literature, but is apparently significantly higher as it reaches 40% in patients with AML diagnosis [8], [9]. Because of being very rare, it is mainly reported some clinical cases in the literature [10].

The therapeutic algorithm for MS is unclear in children and adults. Prospective trials are lacking, therefore treatment recommendations are based on retrospective studies which focus on adult patients. Available treatment options include systemic chemotherapy, surgical resection, radiotherapy, haematopoietic stem cell transplantation (HSCT) or a combination of these methods.

In isolated MS, it is recommended to start AML conventional chemotherapy as soon as possible, as it is known that untreated MS will almost always progress to AML. Chemotherapy includes standard daunorubicin and cytarabine induction therapy, followed by high-dose cytarabine. If the response is not fully achieved, radiotherapy can be considered, as a consolidation therapy.

In MS associated with systemic disease, AML chemotherapy is also recommended, with consideration of alloHSCT, especially if other unfavourable prognostic factors are present (age, cytogenetics). The role of alloHSCT is highlighted in several studies, in which it has been shown that alloHSCT improves the overall survival of patients with MS [11].

The 5-year survival rate for the patients with MS was 21%. The patients undergoing chemotherapy had a significantly longer survival time compared to those who did not ($p = 0.0009$). We found no difference in the 5-year survival rate among the patients undergoing chemotherapy combined with radiation or surgery. Patients with chronic myelogenous leukemia and myelodysplastic disorders had worse survival rates ($p = 0.0028$) [12].

The aim of this study is to introduce a boy with a very rare clinical case of MS in the diagnosis of myelodysplastic syndrome.

PATIENT AND METHOD

Patient: a 9 year old boy, diagnosed as myeloid sarcoma in Pediatric Oncology Department, Viet Nam National Cancer Hospital from May, 2016 to August, 2016.

Method: Case report.

CASE PRESENTATION

Administration

- Name of patient: Nguyen Cong Duc M Year of birth: 2007 Sex: Nam
- Address: Son Ha Village, Thach Son Ward, Thach Ha District, Ha Tinh Province.
- No of profile: 16304768 BV K. Code of patient: 163034252 BV K.
- Date of admission: 12th, May, 2016.
- Date of discharge: 29th, August, 2016.
- Mobile phone of the mother: 0915966313.
- Reason of admission: Postoperative pancreatic tumor from Viet Duc hospital.

History

Before 1.5 months of admission, the patient has epigastric pains, vomiting, no fever in 2 weeks. He has not been examined and treated. After 2 weeks, epigastric pains became more serious→Province hospital: Ultrasound showed a pancreatic mass→Viet Duc hospital: pancreatic mass, a suspected diagnosis of pancreatic adenocarcinoma: The patient was undergone an operation 15th, April, 2016: whipple pancreaticoduodenectomy with regional lymphadenectomy was performed, lách, spleenectomy, appendectomy. Pathology: Mantle non Hodgkin's lymphoma→National Cancer Hospital.

Clinical Examination in Pediatric Oncology Department, National Cancer Hospital

Alert, no fever, no dyspnea, no palpable peripheral lympho nodes and tumors. Soft belly, no ascite, operative scar, no palpable abdominal tumors and lympho nodes, no spleenhepatomegaly, no lesions in kidneys. Normal neuropsychology, heart, lungs...

Family history and medical history: no significant past medical history. The patient was healthy in the past.

Laboratory Tests

Hemomyelogram

Peripheral blood count: Lower red blood cell count and hemoglobin, irregular size, no red blood cell blast count, white blood cell count decreased, neutropenic neutropenia. The amount and concentration of normal

platelets. Bone marrow: The number of marrow cells 40,14 G/L, normal density. Red blood cell rate normal, differentiated, morphology is nothing special. Granulocytes meet all ages, mature, morphologic disorder. Platelet aggregation decreases, monocytes increase, activation of mono. Meet the proportion of blast cells, medium size, large nucleus, coil, nuclear, alkaline, alkaline. Conclusion: Diagnosis of dysplasia. Recommended bone marrow biopsy. Bone marrow biopsy: Bone marrow biopsy, sample 2 mmx6 mm biopsies. There are fewer blood cavities. Size of bone and blood vessels normal. Spinal cell density decreases, uneven distribution, erythropoiesis, neutropenia, mainly metamorphic, morphologic changes. Platelet density decreased. Meet the size of the cell, the boundary between cells clear, proto-narrow, basophilic. No malignant metastasis, very little fibroid. Immunohistochemical stains were performed on the paraffin-embedded sections: Negative to CD3, CD20, CD34, CD117, MPO, CK, TdT. Conclusion: myeloproliferative disorder.

Histological Analysis of the Pancreatic Mass: A Suspect Diagnosis: Non Hodgkin's Lymphoma

It revealed extramedullary myeloid tumoral cells with immunohistochemistry negative for CD3, CD5, CD10, CD20, CD34, CD56, CKAE1/AE3, NSE, PR, CD79a, Bcl6, CD19, CD23, Cyclin D1, Synaptophysin. Positive for CD43, CD68, Ki67 (+ 50%), Bcl2, CD117, MPO. Conclusion: Myeloid sarcoma (in WHO 2008 classification).

Abdominal Ultrasound: hypoechoic and hypodense mass 34 x 44 mm of the liver hilar, postoperative outbreaks.

Confirmed diagnosis: extramedullary myeloid sarcoma /myeloproliferative disorder syndromes.

Treatment: Induction Alexan in 7 days + Daunorubicin in 3 days, High dose Alexan consolidation.

Result of treatment:

- Complete response. Healthy, play well, eating and sleeping well. No clinical signs. Normal laboratory tests. PET/CT: with 18 FDG, dose 5.1 mCi. Serum glucose level: 6.0 mmol/l. Conclusion: There are no malignant lesions in PET/CT.

Discharge: 29th August, 2016. Every 3 months follow up: Healthy.

DISCUSSION

Our patient has epigastric pain, fever, a tumor at the pancreatic head and body and was suspicious of pancreatic carcinoma or non Hodgkin's lymphoma likely in some reports. However, an immunohistochemical panel including some markers could successfully identify the vast majority of extramedullary MS concurrently with a myeloproliferative disorder. We indicated the systemic chemotherapy against the leukemia that is typically used as the first-line treatment. Chien Heng Lin et al (2008) reported an extremely rare case of MS in the colon of a 10-year-old boy with AML presenting with hematochezia. Colonic MS was diagnosed by colonofiberscopic biopsy. His hematochezia responded rapidly to induction chemotherapy and the patient remained in complete remission after 3-month follow-up [13]. Ramesh Murthy et al (2009) describe 12 cases of acute myeloid leukemia that presented to the ophthalmology clinic with proptosis and a diagnosis of AML was subsequently made by a peripheral blood smear or incision biopsy from January, 1998 to September, 2008 [14]. Aalia R Sufi (2011) reported eight years old child who presented with proptosis of right eye with ocular pain and redness over a span of 15 days. A provisional diagnosis of rhabdomyosarcoma was made due to the acute onset of proptosis and young age, rhabdomyosarcoma being the commoner primary orbital malignancy in children. On the basis of the peripheral blood film report, the patient was diagnosed as a case of ocular granulocytic sarcoma in acute myeloid leukemia. Patient received Inj. Arabinoside C 65mg for 7 days and Daun- orubicin 35 mg per day for 3 days. Patient showed drastic regression of proptosis, but developed corneal abscess. The patient returned home and was lost to further follow-up [15].

Binitha Rajeswari et al (2011) reported a one year old female child presented with pancytopenia. A thorough evaluation including bone marrow study did not reveal any definite evidence of malignancy. She presented two months later, with fever, followed by increasing jaundice, pale stools and abdominal distension. She was sick, with severe pallor, jaundice, generalized edema and massive ascites. Hepatosplenomegaly could not be assessed due to the massive ascites. CT scan and ultrasound scan of the abdomen showed a soft tissue lesion 6x4cm wedged between the pancreas and liver. There was moderate bilobar

intrahepatic biliary radicle dilatation and common bile duct dilatation upto pancreatic segments. There was bulky celiac axis, mesenteric and retroperitoneal lymphadenopathy with moderate ascites and bilateral minimal pleural effusion. Flow cytometry analysis done on the ascitic fluid revealed positivity for CD13, CD33, CD117 and CD7 markers, diagnostic of AML, possibly M5. Bone marrow study was deferred due to her poor general condition. The patient was started on subcutaneous cytosine arabinoside. In the following two weeks she improved with clearing of jaundice, reduction of abdominal distension and improvement of blood counts. Despite starting chemotherapy with intravenous cytosine arabinoside and daunorubicin, she developed sepsis and died [16].

There are some reports of adult clinical cases. Xin-Ping Li et al (2011) reported a 48-year-old woman with no significant past medical history. She was referred because of acute abdomen with no history of abdominal trauma. She complained of persistent severe epigastric pain accompanying a high fever for three days, but not of vomiting, diarrhea or shortness of breath. Laboratory test showed 128 U/L aspartate aminotransferase (AST), 270 U/L alanine aminotransferase (ALT), 1365 U/L lactate dehydrogenase (LDH). Computed tomography scan revealed a 4.5 cm × 4.0 cm fuzzy mass at the pancreatic tail with splenomegaly and splenic infarction. Bone marrow infiltration was assessed and no evidence of AML was found. Exploratory laparotomy was performed because of persistent severe abdominal pain. An invasive tumor was detected in the pancreatic tail with lymphadenectasis around the hilus of spleen. Consequently, the patient underwent splenectomy and distal pancreatectomy. Histological examination revealed diffusely infiltrating monomorphous immature blast-like cells. Immunohistochemical staining showed that tumor cells reacted to myeloperoxidase (MPO) antibodies but not to CD20 monoclonal antibodies. A diagnosis of MS was made and intensive AML-type chemotherapy was recommended. Unfortunately, the patient refused further chemotherapy and was discharged from hospital. Follow-up showed an isolated tumor recurred 2 mo after operation and the patient died 3 mo after operation [17].

Mathieu Messenger et al (2012) reported a 45-year-old woman, without significant comorbidity,

who was referred to the institution for surgery. Epigastric pain with jaundice began one month previously without performance status alteration. Based on the symptoms, a suspected diagnosis of pancreatic adenocarcinoma and a resectable mass, it was determined to proceed with primary surgery without obtaining preoperative sample biopsies. Curative whipplepancreaticoduodenectomy with regional lymphadenectomy was performed with no specific peroperative discovery and uneventful postoperative course. Histological examination of the surgical specimen revealed a pancreatic GS based on the presence of cells of myeloid lineage with positive immunostaining for CD43 myeloid-associated antigen. Six weeks later, diffuse relapse occurred with the appearance of left cervical and multiple thoracic lymph nodes. Cisplatin - cytarabin - dexamethasone-based chemotherapy was administered quickly, but the patient died due to disease dissemination one month later. The second patient was a 19-year-old woman, who presented at the institution for epigastric pains combined with hyperamylasemia (1.7 N) and hyperlipasemia (7.8 N). After conventional medical treatment for pancreatitis, the symptoms disappeared. Due to early recurrent epigastric pain episodes, combined with persistent hyperlipasemia, the decision was made to proceed with a surgical exploration. Histological analysis of the pancreatic mass and peritoneal biopsies revealed extramedullar myeloid tumoral cells with immunohistochemistry positive for MPO, CD43, and CD34 as well as CD117 and CD45, and negative for CD79a, CD3, CD2, CD4, CD8 and CD68, leading to the diagnosis of pancreatic GS. The brain CT scan and bone marrow biopsy were normal. An induction cytarabin-based chemotherapy was begun quickly, leading to a complete morphological response after three consolidation cycles. However, recurrence was diagnosed and the patient has undergone second line, third line chemotherapy and leading to palliation [18].

Leena Jayabackthan et al (2014) described a rare case of granulocytic sarcoma of the nasal cavity. The patient was 30 year old male. He had no significant past history. Clinical examination showed a deviation of nasal septum and a mass arising near the middle meatus. A biopsy of the nasal mass was done, subsequent Immunohistochemistry on the biopsy was positive for CD34 and CD117 thus confirming the diagnosis of MS. Bone marrow biopsy and immunohistochemistry

showed blast cells strong positivity for CD 117. The patient was treated with chemotherapy as AML [19].

Semra Paydaş et al (2014) reported 37-year-old man who was admitted to the hospital at December 2010 with fatigue, abdominal pain, and a 10-kg weight loss over 6 months. Abdominal ultrasonography showed a hilar mass of the pancreas, intra/extrahepatic bile duct dilatation, hydropic gallbladder, and splenomegaly. Upper abdominal MRI and MR angiography showed a mass lesion localized at the head of pancreas, invading the superior mesenteric vein and bilateral renal veins with intra/extrahepatic bile duct dilatation. He had a past medical history of intermediate-risk AML 5 years prior to admission. Histopathological exam of the biopsy taken from the duodenal mass revealed myeloid sarcoma. There was no evidence of leukemic infiltration in the bone marrow and biopsy was normocellular. Salvage FLAG-IDA (fludarabine–cytosine arabinoside–idarubicin–G-CSF) chemotherapy was given, but the patient died of neutropenic sepsis 8 months after his first gastrointestinal symptoms [20].

MS presented very clinically variably. Mehrpour Moradi et al (2016) reported a 15 year old girl who was brought to emergency department with acute abdominal pain, vomiting and low-grade fever. Abdominal sonography showed a hypoechoic lesion in right ovary suspicious to hematoma and also splenomegaly was detected. Bone marrow aspiration, immunohistochemistry and flow cytometry were in favor of acute myeloblastic leukemia with maturation (M2). The patient received chemotherapy and she was in remission with good improvement. After taking two course of chemotherapy, abdominal sonography revealed no lesions [21].

Moumita Sengupta et al (2016) reported The 2-year-old male patient who presented with chief complaint of gradually increasing circumscribed swelling in the left side of the body of the mandible for last 1 year. The child used to cry on touching it. There was no other associated complaint. Computed tomography scan of the head and neck region showed a soft tissue mass eroding bone over the body of the left side of mandible. He underwent tru-cut biopsy from the lesion. Histological examination of the specimen showed mononuclear blast-like cells arranged in sheets with thin intervening fibrous septa. Immunohistochemical stain of the paraffin-embedded tissue sections showed that the blast cells were positive for CD45, CD68 and

lysozyme negative for CD3, CD20, CD99, terminal deoxynucleotidyl transferase (TdT), myelo peroxidase (MPO) and CD138. The histological and immuno histochemical findings confirmed the diagnosis of MS with monocytic differentiation. bone marrow biopsy of the patient was done to detect whether bone marrow involvement was present or not but no abnormality was detected at that point of time. The patient was given cytarabine and anthracycline-based induction therapy followed by consolidation with cytarabine alone. On completion of chemotherapy, swelling completely reduced in size. The patient is now being followed up for any local recurrence or systemic relapse at an interval of every 6 months [22].

Pallavi Agrawal và cộng sự (2016) report a 10 year-old-male child was admitted to pediatric unit for complaints of fever and nodules over the left side of face and back for 1.5 months. On examination he had moderate pallor, cervical lymphadenopathy and bluish coloured subcutaneous nodules over face and back. The clinical possibilities of bacterial infection, acute leukemia and lymphoma were considered and the patient was investigated accordingly. Ultrasound abdomen revealed mild hepatomegaly with mild splenomegaly. A bone marrow examination and fine needle aspiration cytology (FNAC) were performed. The bone marrow was normocellular and showed adequate representation of all three hematopoietic lineages. There was no evidence of leukemia, myelodysplasia, myeloproliferative neoplasm and lymphoma involvement with in the bone marrow aspirate and biopsy. On the other hand FNAC smears from the facial swelling were cellular and showed scattered immature mononuclear cells. Sample for flow-cytometry (FCM) was also taken at the same time from these subcutaneous nodules. The FCM examination revealed approximately 22.5% CD 45 positive events which showed presence of myeloid and monocytic markers (CD 45, HLA DR, CD 13, CD 117, CD 11c and CD14) and absence of all lymphoid markers (CD 3, CD5, CD4, CD 8, CD 10, CD19, CD20, CD 22 and CD 79a. A diagnosis of non-leukemic GS was considered. The patient was initiated on chemotherapy as for regular AML with UKMRC-AML protocol (The first induction course included Cytosine Arabinoside, Daunorubicin and Etoposide) and the lesions clinically resolved following the first course of chemotherapy. Unfortunately the patient had died after 2 course of chemotherapy due to febrile neutropenia [23].

CONCLUSION

MS is a rare extramedullary tumor that consists of immature granulocytic cells. It may occur *de novo* or concurrently with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or a myeloproliferative disorder. This tumor can present prior to, concomitantly or even during remission of systemic leukemia. The natural history of these tumors can be variable. In the diagnostic process of MS, the biopsy of the tumour and immunohistochemical staining are most important. If possible, tissue biopsy is preferable to fine needle biopsy [31]. Flow cytometry, cytogenetic and molecular analysis of the tissue are also recommended. Flow cytometry of the peripheral blood and bone marrow is essential, to exclude systemic disease. Since randomized prospective trials are lacking, there is no consensus on the treatment of MS. The current recommended treatment regimen in patients presenting with isolated MS or MS presenting concomitantly with AML is conventional AML-type chemotherapeutic protocols. Nonleukemic GS is a very rare disease and have poor prognosis.

RECOMMENDATION

The correct diagnosis of MS are essential for adequate therapy which is often delayed due to the high misdiagnosis rate. MS are rare neoplasms whose knowledge is largely based on case reports and/or technically dated contributions. There are not enough data currently available to support a risk-adjusted therapy in the setting of isolated MS. Owing to the rarity of this disorder and in order to include larger groups of patients, controlled prospective multicenter studies are necessary.

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