CASE REPORT

Immunoproliferative small intestinal disease versus colonic monoblastic sarcoma in a 2-year-old boy

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Abstract
The authors present a case of colonic monoblastic sarcoma, previously treated for other digestive abnormalities (malabsorption, Hirschprung’s disease). Important similitudes with immunoproliferative small intestinal disease (IPSID) lymphoma were demonstrated for this patient (male, 2-year-old). His main admission complaints were failure to thrive, recurrent episodes of enterocolitis and malabsorption syndrome. Some particularities of this case are the young age and the extremely rapid development of the malignant disease in a patient with no previous signs of acute non-lymphoblastic leukemia. The initial diagnosis was of malabsorption syndrome, based on the clinical exam at presentation, and then the patient was thought to have a form of Hirschprung’s disease, due to a functional intestinal disorder (slow transit). After the necropsy, pathologists diagnosed an immunoproliferative small intestinal disease, and four years later, they performed a more appropriate pathological exam, which explained better clinical symptoms associated to this complex case.

Keywords: immunoproliferative small intestinal disease (IPSID), monoblastic sarcoma, malabsorption syndrome.

Introduction
Extramedullary myeloid tumors, tumor masses consisting of myeloblasts or immature cells in an acute myeloblastic leukemia (AML), have been reported [1, 2]. Clinical features include common occurrence in subperiosteal bone structures of the skull, paranasal sinuses, sternum, ribs, vertebrae and pelvis, lymph nodes, skin, mediastinum, small bowel, and the epidural space; occurrence de novo or concomitant with AML or another myeloproliferative disorder was also described in literature [1, 2].

Morphological and cytochemical features include the following: granulocytic sarcoma, monoblastic sarcoma, tumors with tri-lineage hematopoiesis occurring with transformation of chronic myeloproliferative disorders, myeloblasts and neutrophils positive for myeloperoxidase (MPO), neutrophils positive for naphthol ASD chloroacetate esterase. Some chromosomal abnormalities are associated with myeloid sarcoma like: AML with maturation and t(8;21)(q22;q22) [1, 2] and acute myelomonocytic leukemia (AMML) Eo with inv (16)(p13; q22) or t(16;16) (p13;q22). Monoblastic sarcoma may be associated with translocations involving 11q23 [1]. The presence of myeloid sarcoma in patients with the otherwise good-risk t(8;21) AML may be associated with a lower complete remission rate and decreased remission duration [3]. Myeloid sarcoma occurring in the setting of myelodysplastic syndrome (MDS) or myeloproliferative disease (MPD) is equivalent to blast transformation. In the case of AML, the prognosis relies on the corresponding type of leukemia [1]. Although the initial presentation of this sarcoma may appear to be isolated, several reports indicate that “isolated” myeloid sarcoma is a manifestation in a systemic disease and should be treated with intensive chemotherapy [2, 4, 5].

Patient, Methods and Results
We present the case of a 2-year-old male patient with a confusing history and an uncertain moment of onset, initially admitted to Intensive Care Unit at “St. Mary” Emergency Children’s Hospital in Iassy, being transferred from another district hospital; his disease seemed to start for two months with diarrhea, vomiting and anorexia; he had received antibiotic treatment (Gentamycin, Cephtriaxone, Colimycin), with an unfavorable course of the disease. In the Intensive Care Unit, the patient maintained a critical condition, with intermittent fever, enlarged liver, 3.5 cm under the ribs edge, slow intestinal transit.

Laboratory tests: the number of white blood cells oscillated between 4000/mm³ and 11 800/mm³, which
was explained by an episode of acute bronchiolytis, sustained by the radiological aspect (bilateral interstitial infiltrate, with generalized emphysema). The leukocyte smear showed lymphocytosis. Hemoglobin values varied between 9 mg/dL and 13 mg/dL, with 80‰ reticulocytes, the patient having had a regenerative hypoferremic anemia. The erythrocyte sedimentation rate registered levels between 16 mm/1 hr. and 90 mm/1 hr., with fibrinogen between 1.9 and 3.2 mg%. Because of recurrent infections a suspicion of humoral immunity deficit was raised, but this was not sustained by the normal values of protein electrophoresis (total proteins – 70.3 mg/L, albumins 33.7%, α1 – 4.3%, α2 – 7.9%, β – 3.8%, γ – 18.6%) and immune electrophoresis (IgA – 88 mg/dL, IgM – 360 mg/dL, IgG – 236 mg/dL). A diagnosis presumption of mucoviscidosis was also invalidated by a normal Na⁺ and Cl⁻ values at iontophoresis (Na⁺ – 14 mEq/L, Cl⁻ – 13 mEq/L), and α1-antitripsine deficit was not considered as a realistic possibility due to a normal value (208 mg%) of α1-antitripsine.

The digestive side effects of the treatment were most probable the main cause of a toxic hepatitis (TGP – 74 IU, TGO – 60 IU). The toxic etiology was confirmed as viral etiology was invalidated (HBs Ag, anti-VHC antibodies, anti-HIV antibodies, anti-cytomegalovirus antibodies were negative).

Stool exam: extracellular starch, lipids, absence of muscle cells. Occult bleeding test was positive. Stool cellularity and cultures were normal as well as urine exam, ASTRUP parameters.

Abdominal ultrasonography examination: liver with a homogeneous increased reflectogenic echostructure, right hepatic lobe – 90 mm, left hepatic lobe – 52 mm, enlarged gallbladder, with thickened walls, without concretions, normal spleen, normal right kidney, medium enlarged left kidney.

The first bone X-ray indicated diffuse osteoporosis in the hand and forearm bones, the patient’s bone age being similar to that of a normal 1-year-old patient.

The unfavorable evolution, despite treatment, required superior digestive endoscopy with jejunal mucosa biopsy. The endoscopic aspect was that of a normal esophagus, normal, permeable cardia, stomach with a normal caliber, normal peristaltis and pale mucosa, normal duodenum.


Mucosal biopsy: lympho-plasmocytic infiltrate with moderate flattening of the intestinal villosities (Figure 1).

Abdominal radiography demonstrated the existence of hydroaeric levels in the superior and inferior quadrants of the abdomen. These features, associating clinical state of the patient (swollen, painful, large abdomen, with collateral circulation, without peritoneal irritation though, with presence of stools at rectum exam, normal Douglas recessus and with the irigography aspects (dilated ascendent, transverse and superior third of the descendent colon), quite patognomonic for Hirschprung, oriented transfer to Pediatric Surgical Unit, where median supraombilical and subombilical laparotomy was performed. During the surgery, massive mesenteric adenopathies and thickening of the intestinal wall were noticed and biopsies were prelevated.

Postoperatory state was critical: with 40°C fever, irreducible tachycardia, intense dyspnea, then progressive bradycardia and cardio-respiratory arrest, irreversible to resuscitation.

Bacillus Koch tests were made and direct lymph nodes imprint cellularity exam showed lymphocytes, very few polymorphonuclears, absence of BK in Ziehl-Nielsen stain: cultures revealed coagulase-negative Staphylococcus albus and enterococcus. Mesenteric lymph nodes biopsy: atypical lympho-plasmocyte infiltrate with large cells and immunoblastic cells (Figures 2 and 3).

Pathology indicated a diffuse malignant lymphoid infiltrate in the small intestinal wall, without any free interval of normal mucosa (Figures 4 and 5).

The same infiltrate was in stomach, bowel, and pericardium (Figure 6).
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Figure 3 – Lymph node: lymphocyte and plasmocytes infiltrate, areas of immunoblastic tumoral cells (HE stain, ×40).

Figure 4 – Small intestine: tumoral infiltrate (HE stain, ×40).

Figure 5 – Small intestine: tumoral infiltrate (HE stain, ×400).

Figure 6 – Colon tumoral infiltrate (HE stain, ×100).

Immunohistochemistry: L26-; UCHL+ in few cells; CLA+ in some areas; EMA-; PCNA+ in 30% of tumoral cells; IgM++; IgA+/-; IgG-; Light chain κ/λ = 5/1; CD68- (Figure 7). At this time, pathological diagnosis was that of an immunoproliferative small intestinal disease. Four years later, in 2002, we rechecked the case according to the new WHO Classification and applied new immunostaining at “St. Jude” Research Children’s Hospital, Memphis (USA). We studied this case with a new set of markers CD20 for B-lymphocyte, which was negative (Figure 8), for T-lymphocyte: CD3 and CD5 – both negative. For the myeloblastic line: myeloperoxidase MPO-negative (Figure 9), keratin-negative in the tumoral infiltrate and positive in the mucosal epithelium (Figure 10), vimentin-positive, CD45 (LCA) positive (Figure 11).

Figure 7 – Light chain κ (×100, left) and λ (×100, right).

Figure 8 – CD20-negative, ×200.
Monocyte markers: CD68-positive (Figure 12), lysozyme-positive (Figure 13). The final diagnosis was that of monoblastic sarcoma (WHO Classification), the monoblastic variant of myeloid sarcoma.

**Discussion**

Our first conclusion was that the clinical behavior and morphological pattern of this B-cell proliferation can include it in the IPSID lymphoma (Immunoproliferative Small Intestine Disease).

The term IPSID (WHO, 1975) defines a diffuse, benign or malignant lymphoid infiltrate, affecting the mucosa of the small intestine, without any free interval of normal mucosa. IPSID include: alpha-heavy chain disease, the Mediterranean lymphoma (described before alpha-heavy chain disease) and non-secretory alpha-chain disease. Clinical, IPSID is a poorly recognized cause of malabsorption syndrome.

Myeloid sarcomas [6, 7] are extramedullary collections of neoplastic myeloid precursor cells. Different names including chloroma (a term initially used because of the tumor’s transient green appearance, which fades on exposure to oxygen), granulocytic sarcoma, and extramedullary myeloid tumor (a term that describes extramedullary and extracranial collections of myelocytic precursors) have been used to describe this condition [8, 9].

Although a small number of myeloid sarcoma occur de novo (in the absence of acute myeloid leukemia, myelodysplastic syndrome, or myeloproliferative disorder in a bone marrow biopsy within 30 days of the diagnosis of myeloid sarcoma), most of them accompany bone marrow involvement of a myelodysplastic syndrome or a myeloproliferative disorder, most commonly acute myeloid leukemia. The lesion also provides evidence of relapsed acute myeloid leukemia. Occasionally, there may be a prolonged interval (months to years) between the occurrence of myeloid sarcoma and acute myeloid leukemia.
Myeloid sarcomas may arise almost anywhere in the body. Subperiosteal tissue of the skull and paranasal sinuses, sternum, ribs, vertebrae and pelvis are the most common sites. The skin and lymph nodes are also affected. Children up to the age of 16 years with acute myeloid leukemia have a proportionately higher incidence of orbital myeloid sarcoma compared to adults [10]. Children with acute myelomonocytic leukemia also seem to have a higher incidence of orbital involvement with exophthalmos, chemosis and orbital masses as symptoms [11].

The overall incidence of myeloid sarcoma is difficult to be assessed because of lack of uniform biopsy standards and uncertain correlation with abnormal physical findings. Retrospective studies report an incidence between 3% and 20% (in a study that described only meningeal leukemias). The incidence reports varied based on the ages of the patients studied and sites excluded from the analysis (most commonly skin or meninges) [11]. Myeloid sarcomas, in general, occur in a relatively larger percentage of children with acute myeloid leukemia, particularly infants (<2-year-old). Patients with myeloblastic and monoblastic (French–American–British (FAB) M4) and monoblastic (FAB M5) leukemia tended to have a higher incidence of myeloid sarcoma, particularly leukemia cutis and gingival involvement, than patients in other FAB classifications [11–14].

**Pathology**

There are two major types of myeloid sarcoma: the granulocytic sarcoma and monoblastic sarcoma. The immature type is composed of a mixture of myeloblasts and promyelocytes. The monoblastic sarcoma is predominantly composed of monoblasts.

The diagnosis of acute myeloblastic leukemia (AML–M5) is based on cell morphology, cytogenetics, molecular anomalies, cellular markers and clinical information. The monoblastic sarcoma is the extra-medullary form of AML–M5, an invasive, destructive tumor, composed of immature myeloid tumor cells.

Frequency: 5–8% of AML cases, 15–25% of pediatric AML cases.

Locations: bone, lymph nodes, gastrointestinal tract, breast, tonsils, skin, pericardium, spine, central nervous system.

Histological aspect: macroscopically – firm green tumors, microscopically – myeloblasts, few myelocytes and mature granulocytes.

The positive diagnosis is established by tumor cell morphology, MPO, lysozyme, cytogenetics, molecular genetics: 4% t(9;11)(p22;q23).

In the leukemogenic mechanisms are: MLL (myeloid lymphoid leukemia) gene fusion 11q23 with AF9p21 gene, resulting in MLL–AF9 gene. 1% of cases have t(8;16)(p11;q11) fusion MOZ–CBF.

Tumors with tri-lineage hematopoeisis, a predominance of erythroid precursors, or a predominance of megakaryocytes may occur in conjunction with transformation of chronic myeloproliferative disorders [7]. Imprints are helpful for diagnosis, particularly for preoperatory decisions.

**Immunohistochemical and/or histochemical demonstration for the presence of myeloperoxidase, lysozyme and chloroacetate esterase are mandatory for identification of their myeloid origin.** An immunohistochemical profile is also helpful in subtyping these tumors [15, 16]. Genetic translocations observed in acute myeloid leukemia may also be demonstrated in myeloid sarcomas. Frequently, a translocation between chromosomes 8 and 9, involving 9p21. T(8;9) has an association with chronic myelogenous leukemia [17]. Association of myeloid sarcoma with acute myeloid leukemia with maturation and t(8;21)(q22;q22) and acute myelomonoblastic leukemia with abnormal eosinophils with inv(16)(p13p22) and (p16;16)(p13;q22) may occur [7].

**Differential diagnosis**

The differential diagnosis for myeloid sarcoma includes Langerhans’ cell histiocytosis (particularly in those cases, which have a prominent eosinophilic infiltrate), lymphomas (particularly diffuse large B-cell lymphoma), and peripheral neuroectodermal tumor/Ewing’s sarcoma.

Langerhans’ cell histiocytosis may be considered in the differential diagnosis, particularly when the tumor has an eosinophilic infiltrate. The degree of pleomorphism in Langerhans’ cell histiocytosis is usually less prominent than myeloid sarcoma and their characteristic oval nuclei with longitudinal grooves, the so-called “coffee bean” appearance, allow morphologic separation between the two entities. The Langerhans’ cells are also positive for S-100 protein and CD1a.

Various types of lymphoma may be extremely difficult to be differentiated from myeloid sarcoma. Demonstration of myeloid phenotype is critical for the distinction [18, 19]. In soft tissue sites traditionally known to harbor lymphoma (e.g. testes or lymph nodes) concurrent immunohistochemistry or flow cytometry frequency is helpful in making the diagnosis of lymphoma as well as a battery of immunohistochemical stains, including lymphocyte common antigen (CD45) or a B-cell marker such as CD20.

Peripheral neuroectodermal tumor/Ewing’s sarcoma is one of the “small blue cell tumors” and is the second most frequent solid bone tumors among children and adolescents. Clinical and radiographic correlation is extremely important for the correct diagnosis of this lesion. In more than 85% of cases, the fusion gene EWS/FLI–1 from t(11;22) may be identified from cytogenetic analysis or polymerase chain reaction. The tumor expresses CD99.

**Treatment**

With appropriate chemotherapy (as in acute myeloid leukemia), surgery and stem cells transplantation, long-term remissions can be achieved, despite the aggressive nature of the disease.

**Conclusions**

The differential diagnosis of tumoral masses in young age may be very challenging when we rely on insufficient laboratory means. An appropriate immuno-
histochemistry can avoid confusion like in situations when classical morphology only is provided. This patient’s course of disease was fast and no other involvement of ANLL signs added from onset until the end. Every step in investigation of this uncommon involvement of ANLL signs added from onset until the patient’s course of disease was fast and no other when classical morphology only is provided. This histochemistry can avoid confusion like in situations when classical morphology only is provided. This patient’s course of disease was fast and no other involvement of ANLL signs added from onset until the end. Every step in investigation of this uncommon involvement of ANLL signs added from onset until the patient’s course of disease was fast and no other

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