An atypical promyelocytic sarcoma in a pleural effusion: efficacy of ATRA/ATO treatment

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April 23, 2023

Abstract

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Abstract

Myeloid sarcoma is a rare extramedullary tumoral infiltration of immature myeloid cells and can occur in different sites of the body, without leukemic infiltration A 38-year-old woman patient presented at emergency with a pleural effusion and bicytopenias. In the following days, she worsened with a chylothorax and pancytopenias.

Pleural puncture cytologically revealed promyelocytes with Auer rods. Cytogenetic and molecular analyses subsequently confirmed the presence of the t(15:17) translocation. However, no circulating phase of these atypical promyelocytes was found. Similarly, no other origin was identified.

We conclude that the patient had a myeloid sarcoma of unknown etiology in the form of a pleural effusion with pathological promyelocytes. The patient was treated with a combination of oral all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) with a cytological and molecular remission persisting 3 months after diagnosis.

We report here the first case of a promyelocytic myeloid sarcoma of pleural origin without concomitant evidence of acute promyelocytic leukemia. We also show the efficacy of ATRA/ATO treatment in this etiology.

Abstract word count: 166 / Manuscript word count: 984

Number of references: 5. / Number of figures and tables: 2

Number of supplemental illustrations/tables: No

What is the new aspect of your work?

This is the first case of a promyelocytic sarcoma diagnosed on pleural effusion

What is the central finding of your work?

Promyelocytic sarcoma could be treated by ATRA/ATO based therapy like APL

What is the specific clinical relevance of your work?

Patient with promyelocytic sarcoma have a good and well tolerated answer to ATRA/ATO based treatment.

The data that support the findings of this study are available from the corresponding author, AA, upon reasonable request.

The research leading to these results has not received funding.

All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

There is no ethics approval statement for this case report.

We have obtained the informed consent from the patient.

There is no required permission to reproduce material from other sources nor clinical trial registration to this case report.

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy

Myeloid sarcoma (MS), also known as granulocytic sarcoma or chloroma, is a rare extramedullary tumoral infiltration of immature myeloid cells that can occur in different sites of the body, without leukemic infiltration of the bone marrow (which however can be observed subsequently). The most common affected sites are skin, lymph nodes, gastrointestinal tract, bone, soft tissues, and testes. MS is characterized by a slight male predominance (sex ratio 1.2:1) and affects patients at any age. MS may develop de novo or in association with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), myelodysplastic/myeloproliferative neoplasms (MDS/MPNs). It could be detected months or years before the myeloid malignancies. MS can also be the initial manifestation of relapse in patients treated for AML while in remission[1]. Without intensive chemotherapy, most patients with MS have a higher risk to develop AML in association with shorter survival[2]. Some cases were reported in literature of MS with t(15;17) promyelocytes. APL with MS as the initial presentation where the most common infiltrated sites were spine, skin and tongue[3]. All evolved in Acute promyelocytic leukemia (APL) and combination ATRA-ATO was made, the reference to treat APL[4].

We report here the first case of de novo myeloid sarcoma arising from abnormal promyelocytes with t(15;17) (q24;q21) diagnosed on pleural fluid.

A 38-year-old woman was admitted in emergency for dyspnea and neutropenia. She had a history of Gorham's disease with lytic pelvis involvement. Three years ago, she was diagnosed with an invasive ductal carcinoma HER2+ of the left breast. She was initially treated by a combination of Epirubicin and Cyclophosphamide (4 cycles of EC) followed by Taxol plus Trastuzumab®. Subsequently, she had a mastectomy, parietal radiotherapy and hormonal maintenance therapy since. A rapidly -in two weeks- progressive dyspnea revealed a right pleural effusion without pulmonary embolism. A chylous pleural effusion was diagnosed with no sign of bacterial infection neither presence of breast malignant cells. CA 15-3 dosage was normal.

The patient also presented bicytopenia with neutrophils = 1.7 x 109/L and hemoglobin = 11.3 g/dL without abnormal circulating cells. On the following days, a thrombocytopenia appeared (platelets = 136 x 109/L). Haemostasis tests showed (Table 1) normal value of prothrombin time (PT), normal fibrinogen, increased D-dimers (Ddi) and prolonged activated partial thromboplastin time (aPTT) related to prophylactic heparin treatment. A sternal bone marrow (BM) aspiration was realized on D10 but it was non contributive due to hemodilution. No qualitative cytological abnormality on blood smear was noticed. We performed Next-Generation Sequencing (NGS) on BM sample which did not detect any mutation. Taken together, these results did not allow us to identify the origin of cytopenias.

On D13, another pleural puncture was carried out: a lactescent, hemorrhagic, and sterile liquid was collected with 1100 leucocytes/µL. Cytological analysis revealed a granulocytic contingent composed of promyelocytes containing intense azurophilic granulations and bundles of Auer rods (Fig 1a & 1b). These results suggested an extramedullary location of promyelocytic acute myeloid leukemia (APL). Flow cytometric analysis performed on this sample revealed an immature myeloid population expressing CD45dim, CD117, CD33, CD13 and partially CD7 whereas CD34 and HLA-DR were negative. Fluorescence in situ hybridization (FISH) confirmed the presence of a t(15;17) (q24;q21) translocation in 20% of the analyzed nuclei (Fig 1c). Results of molecular biology subsequently confirmed the presence of the fusion transcript *ΠΜΛ-PAPA* (bcr2 breakpoint) at high level in the pleural effusion sample whereas blood and bone marrow samples were negative.

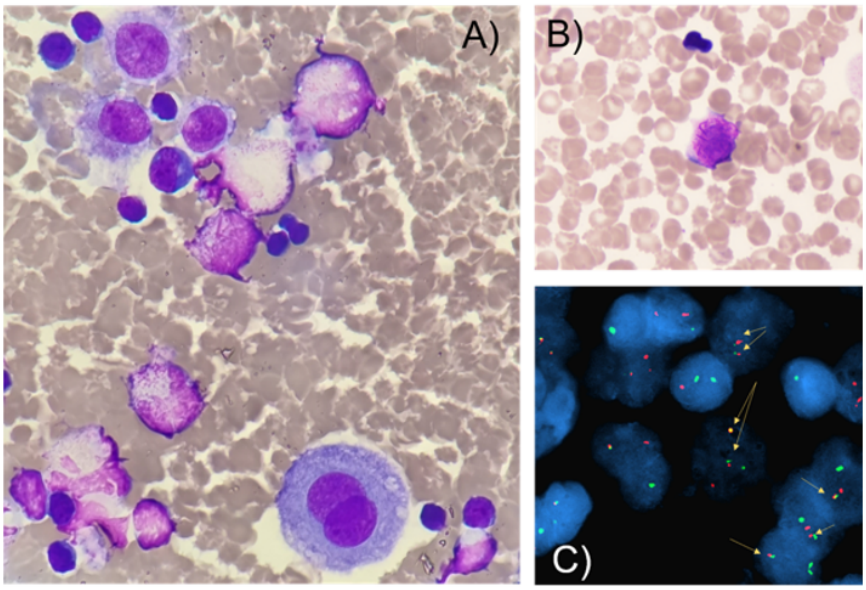

FIGURE 1

(A) MGG stained cytospin (50X) from pleural puncture at D13 showing a pathological promyelocyte with Auer rods in a mixed inflammatory cells infiltrate including mesothelial cells and lymphocytes (B) MGG stained smear from the pleural puncture (50X) showing another pathognomonic APL promyelocyte with numerous Auer rods (C) FISH analysis with PML and RARA double fusion probes demonstrating the presence of *PML-RARA*fusion rearrangement.

Gorham's disease is a rare disorder of unknown etiology characterized by massive osteolysis, angiomatosis involving blood vessels and more rarely lymph vessels[5]. Bone involvement is variable and can lead to destruction of osseous matrix. Pleural effusions or chylothorax may occur. Our patient was affected by a disabling osteolysis of pelvic bone treated by bisphosphonates which contraindicated iliac bone marrow puncture or biopsy. The previous thoracic radiotherapy and the angiogenesis associated with Gorham's disease, may explain the recurrent non contributive diluted sternal aspirations. Blood molecular tests did

not allow us to confirm the diagnosis of APL, NGS myeloid panel did not detect any somatic mutation in agreement with the absence of abnormal circulating cells. FISH analysis performed on D10 BM puncture was negative for *PML-RARA* fusion.

Considering the absence of circulating blasts and the observation of typical pathological promyelocytes only in the pleural fluid, the diagnosis of myeloid sarcoma (extramedullary APL) was retained. On D17, oral all-trans retinoic acid (ATRA) treatment 45 mg/m^2/day (60 mg) was started with addition three days later of arsenic trioxide (ATO) 0.15 mg/Kg intravenous over 2 hours daily according to APL0406 protocol. Treatment was well tolerated.

Pleural fluid collected at D27 revealed differentiated granulocytic cells with persistent Auer rods, hypergranular cells and a significant eosinophilic contingent up to 35% of putative reactive origin. Thereafter, we confirmed the absence of pathological cells on two consecutive pleural punctures realized at D33 and D38. The treatment by ATRA/ATO combination was thus found to be well tolerated and efficient in our patient. Three months after the diagnosis, the patient was in cytological and molecular remission. She had oral ATRA (70 mg/day) 2 weeks per month as consolidation treatment.

BM sternal puncture was not contributive due to Gorham's disease, and it could not be repeated on iliac crest due to the osteolysis associated with this disease. When myeloid sarcoma is diagnosed in association with bone marrow leukemic infiltration in favor of APL, a circulating phase with the presence of blasts should be observed in association with t(15;17) (q24;q21) translocation and the presence of the *PML-RARA*fusion transcript. In our case, no involvement of peripheral blood and diluted BM were observed. However, the demonstration of characteristic promyelocytes, without concomitant circulating blasts, nor cytogenetic anomaly or molecular criteria on blood and diluted BM, was in the line with the diagnostic of de novo MS without concomitantly APL. Due to therapeutic emergency of this clinical presentation, ATRA-ATO based chemotherapy should be required, and has been rapidly initiated with success and good tolerance.

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TABLE 1

Blood parameters	**Reference values**	**11/09/2022 On admission**	**30/09/2022 D19**	**12/10/2022 D31**	**03/11/2022 D53**	**14/11/2022 D64**
White Blood Cell (WBC) count	4.0 – 10.0 x 10^9/L	1.7 x 10^9/L	3.1 x 10^9/L	2.0 x 10^9/L	2.5 x 10^9/L	5.3 x 10^9/L
Hemoglobin	11.5 – 15.0 g/dL	11.3 g/dL	11.9 g/dL	9.8 g/dL	8.9 g/dL	9.9 g/dL
Hematocrit	34.0 – 45.0%	32.3%	35.1%	29.6%	25.2%	29.9%

Blood parameters	Reference values	11/09/2022 On admission	30/09/2022 D19	12/10/2022 D31	03/11/2022 D53	14/11/2022 D64
Mean Corpuscular Volume (MCV)	75.0 – 96.0 fL	92.0 fL	96.4 fL	99.0 fL	97.3 fL	105.3 fL
Mean Corpuscular Hemoglobin (MCH)	24.0 – 33.0 pg	32.2 pg	32.7 pg	32.8 pg	34.4 pg	34.9 pg
Mean Corpuscular Hemoglobin Concentration (MCHC)	32.0 – 36.0 g/dL	35.0 g/dL	33.9 g/dL	33.1 g/dL	35.3 g/dL	33.1 g/dL
Reticulocytes	25.0 – 100 x 10^9/L	/	131.4 x 10^9/L	/	368.1 x 10^9/L	341.4 x 10^9/L
Platelets	150 – 450 x 10^9/L	152 x 10^9/L	150 x 10^9/L	189 x 10^9/L	285 x 10^9/L	250 x 10^9/L
Absolute Neutrophil Count (ANC)	1.5 – 7.0 x 10^9/L	0.8 x 10^9/L	1.6 x 10^9/L	0.8 x 10^9/L	1.7 x 10^9/L	4.0 x 10^9/L
Absolute Lymphocyte Count (ALC)	1.2 – 4.0 x 10^9/L	/	1.4 x 10^9/L	0.5 x 10^9/L	1.4 x 10^9/L	0.6 x 10^9/L
Absolute Monocyte Count	0.2 – 0.8 x 10^9/L	/	0.1 x 10^9/L	0.1 x 10^9/L	0.2 x 10^9/L	0.4 x 10^9/L
Lactate Dehydrogenase (LDH)	< 246 U/L	237 U/L	173 U/L	209 U/L	162 U/L	221 U/L
Sodium	133 – 145 mmol/L	141 mmol/L	139 mmol/L	139 mmol/L	128 mmol/L	138 mmol/L
Potassium	3.4 – 4.5 mmol/L	2.8 mmol/L	3.5 mmol/L	4.4 mmol/L	3.8 mmol/L	4.2 mmol/L
Chloride	99 – 111 mmol/L	107 mmol/L	107 mmol/L	109 mmol/L	101 mmol/L	109 mmol/L
CO_2	20 – 31 mmol/L	21 mmol/L	25 mmol/L	28 mmol/L	23 mmol/L	22 mmol/L
Blood urea nitrogen (BUN)	3.2 – 8.2 mmol/L	3.4 mmol/L	3.5 mmol/L	6.0 mmol/L	6.5 mmol/L	7.0 mmol/L
Creatinine	44 – 71 µmol/L	43 µmol/L	47 µmol/L	55 µmol/L	28 µmol/L	30 µmol/L
Calcium	2.18 – 2.60 mmol/L	2.52 mmol/L	2.11 mmol/L	2.00 mmol/L	1.68 mmol/L	1.81 mmol/L

Blood parameters	Reference values	11/09/2022 On admission	30/09/2022 D19	12/10/2022 D31	03/11/2022 D53	14/11/2022 D64
Alanine Transaminase (ALT)	< 40 U/L	23 U/L	< 9 U/L	33 U/L	11 U/L	23 U/L
Aspartate Aminotransferase (AST)	< 40 U/L	26 U/L	14 U/L	36 U/L	22 U/L	31 U/L
Prothrombin Time (PT)	70-100%	86%	96%	90%	87%	100%
activated Partial Thromboplastin Time (aPTT)	< 1.2	1.4	1.8	3.2	1.0	0.9
Fibrinogen	2.0-4.0 g/L	2.3 g/L	2.1 g/L	1.8 g/L	1.4 g/L	2.6 g/L
FV	70-120%	/	132%	143%	121%	/
D-dimer	0-0.50 µg/mL	/	11.5 µg/mL	/	3.98 µg/mL	/
C-reactive protein (CRP)	< 10 mg/L	4 mg/L	/	32.7 mg/L	< 4 mg/L	/
Protein	57 – 82 g/L	/	58 g/L	46 g/L	/	37 g/L
Albumin	36.8 – 48.9 g/L (55.8 – 66.1%)	/	31.7 g/L (54.9%)	27.2 g/L (58.9%)	/	22.0 g/L (59.9%)
Alpha-1 globulin	1.9 – 3.6 g/L (2.9 – 4.9%)	/	3.3 g/L (5.8%)	3.2 g/L (6.9%)	/	2.8 g/L (7.5%)
Alpha-2 globulin	4.7 – 8.7 g/L (7.1 – 11.8%)	/	7.0 g/L (12.2%)	6.5 g/L (14.1%)	/	4.9 g/L (13.4%)
Bêta-1 globulin	3.1 – 5.3 g/L (4.7 – 7.2%)	/	3.6 g/L (6.2%)	1.8 g/L (4.0%)	/	2.7 g/L (7.3%)
Bêta-2 globulin	2.1 – 4.8 g/L (3.2 – 6.5%)	/	2.8 g/L (4.8%)	2.2 g/L (4.7%)	/	1.5 g/L (4.2%)
Gamma globulin	7.3 – 13.9 g/L (11.1 – 18.8%)	/	9.3 g/L (16.1%)	5.3 g/L (11.4%)	/	2.8 g/L (7.7%)