Hypereosinophilia as a paraneoplastic feature of a retroperitoneal sarcoma. Diagnosis difficulties

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ABSTRACT
We present the case of a male patient with hyperleucocitosis (L>140 x 10^9/L) and high eosinophilia (E=78%) related to a retroperitoneal sarcoma. The main entities considered as differential diagnosis were Chronic Eosinophilic Leukemia (CEL) and secondary hypereosinophilia due either to a malignant T-cell lymphoma or to a non-hematologic neoplasm. Both the absence of FIP1L1/PDGFRA (evaluated by RT-PCR) and the lack of response to Imatinib mesilate, supported the diagnosis of secondary hypereosinophilia. The post mortem examination revealed a giant retroperitoneal tumor with multiple secondary locations and confirmed the diagnosis of sarcoma. Although the clinical and biological picture and the initial response to Imatinib therapy may suggest a primary hematological disease, the molecular examination proves its superiority in establishing the correct diagnosis of a hypereosinophilia.

Key words: hypereosinophilia, chronic eosinophilic leukemia, cytogenetic examination, FIP1L1-PDGFRA fusion gene

INTRODUCTION
Hypereosinophilia (AEC>1.5 x 10^9/L) may appear as reactive eosinophilia with multiple causes, as idiopathic hypereosinophilic syndrome (HES) or as chronic eosinophilic leukemia (CEL) (1). The differential diagnosis claims to exclude all the possible causes of secondary eosinophilia (infectious diseases, allergic reactions, immune causes and underlying neoplastic diseases) and implies determining the
markers of clonal myeloid disorder (e.g. the presence of the FIP1L1/PDGFRα fusion gene) that confirm the diagnosis of CEL; idiopathic HES is diagnosed if none of these conditions are fulfilled (1,2).

The correct diagnosis is essential for treatment decision as it has already been demonstrated that Imatinib mesilate induce complete remission in CEL and HES but not in secondary hypereosinophilia. However, some papers showed that negative FIP1L1/PDGFRα fusion gene, did not rule out response to TKI therapy as long as partial and even complete responses were achieved in isolated cases (3).

**CASE REPORT**

A 53 years old male patient was admitted to our clinic with hyperleucocytosis (WBC>140000/mmc) and marked eosinophilia (E=78%). The patient’s performance status was very low, he had fever from time to time, permanent sweats and lost almost 25 kg in the last 4 months. He complained of shortness of breath, back pain, diarrhoea and abdomen enlargement. He had an extensive eritematous rash with pruritus on his arms, legs and thorax, palpable peripheral and abdominal lymph nodes, massive liver and spleen enlargement and minimal pleural effusion.

**Laboratory results at the time of hospital admission:**
- Hyperleucocytosis (WBC=143 x 10⁹/L) and eosinophilia (E=74%) in different stages of maturation, some of them with hypersegmented nuclei and vacuolated cytoplasm (see FIGURES 1,2); mild anemia (Hb=10.0g/dl); thrombocytopenia (Plt=36 x 10⁹/L).
- Liver function tests showed increased values for cholestasis enzymes (ALKP=4 x normal values and GGT= 6 x normal values) but normal levels of AST and ALT; LDH was 8 times normal and serum albumin was low.
- Vitamin B12 was high (1.5 x normal values).
- Bone marrow aspiration: 2% myeloblasts and 50% eosinophils in different stages of maturation, with hypersegmented nuclei, vacuolated cytoplasm, some of them with double types of granules (see FIGURES 3,4).
- Bone marrow biopsy: hypercellular marrow with increased number of immature granulocytes, hypereosinophilia and frequent eosinophilic myelocytes and metamyelocytes; no metastatic cells were identified.
- Cytogenetic examination: no evidence of Ph chromosome
- Qualitative real-time RT-PCR was performed for bcr-abl major form and for abl as a positive control. The result was negative. PCR reactions were followed in real-time using an ABI SDS7700 TaqMan PCR machine. We mention that all the molecular assays (RT-PCR for FIP1L1/PDGFRα fusion gene) were performed at Munster University, Germany, by the courtesy of Dr Anca Ilea from Ritus Biotec laboratory.
- CT scan (chest and abdomen): multiple pleural and pulmonary nodules, small left pleural effusion, lymph node enlargement all around the aorta and esophagus (see FIGURES 5,7); a giant left renal region tumor with retroperitoneal extension into left psoas muscle, that includes the superior mesenteric artery and celiac trunk; thrombosis of the left renal vein; multiple necrotic adenopathies; enlarged liver with metastatic nodules of maximum 70mm diameter (see FIGURE 6).
- Echocardiography: diffuse hypokinesia, tricuspid regurgitation, mild pulmonary hypertension, ejection fraction 45%
- Doppler echography of the abdominal veins: confirms the left renal vein thrombosis but not of the inferior cava vein that seems compressed by the tumor

The main entities considered as differential diagnosis in this case were Chronic Eosinophilic Leukemia (CEL) and secondary hypereosinophilia due either to a malignant T-cell lymphoma or to a non-hematological neoplasm. We present in TABLE 1 the most important reasons of the differential diagnosis:

Although the clinical picture was suggestive for a hematological disease like a myeloproliferative disorder accompanied by primary eosinophilia (e.g. chronic eosinophilic leukaemia) or by secondary eosinophilia (e.g. a myeloid of lymphoid neoplasm with eosinophilia), the CT scan raised the suspicion of a non-hematological malignancy, most probably a retroperitoneal tumor with multiple secondary metastasis while the excessive eosinophilia appears as a paraneoplastic manifestation.
### 1. Chronic Eosinophilic Leukemia

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<td>- skin rash</td>
<td>- no evidence of blasts in peripheral blood and blasts in bone marrow &lt;5%</td>
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<td>- asthma-like dispnea</td>
<td>- negative RT-PCR for FIP1L1/PDGFRα fusion gene</td>
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<td>- pulmonary infiltrates and pleural effusion</td>
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<td>- diarrhea</td>
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<td>- liver and spleen enlargement</td>
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<tr>
<td>- hyperleucocytosis with marked eosinophilia</td>
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<tr>
<td>- Vacuolated, hypersegmented, hypogranular eosinophils</td>
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<td>- increased levels of Vitamin B12</td>
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### 2. Secondary hypereosinophilia (solid tumor or T-cell non-Hodgkin lymphoma)

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<td>- giant abdominal tumor with secondary metastasis in lung, liver, lymph nodes</td>
<td>- very high leucocytosis and eosinophilia</td>
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<tr>
<td>- negative cytogenetic and molecular assays</td>
<td>- thrombocytopenia without evidence of bone marrow metastasis or DIC</td>
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<td>- increased values of Vitamin B12</td>
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**TABLE 1.** Differential diagnosis

**FIGURE 1.** Peripheral blood – leucocytosis and eosinophilia (MGG, 20x)

**FIGURE 2.** Peripheral blood – eosinophils with hypersegmented nuclei and vacuolated cytoplasm, some of them with few granules (MGG, 100x)
HYPEREOSINOPHILIA AS A PARANEOPLASTIC FEATURE OF A RETROPERITONEAL SARCOMA

FIGURE 3. Bone marrow aspirate with eosinophils in different stages of maturation (MGG, 100x)

FIGURE 4. Bone marrow aspirate with immature eosinophils (MGG, 100x)

FIGURE 5. Chest X-Ray: secondary pleural and pulmonary nodules
FIGURE 6. Abdominal CT scan – retroperitoneal tumor with hepatic metastasis

FIGURE 7. Chest CT scan – multiple pulmonary nodules; pericardial and pleural effusion
The cytogenetic and molecular assays (that excluded a myeloproliferative neoplasm) and the immunophenotyping of the peripheral T lymphocytes (that couldn’t identify any clonal population) elucidated the diagnosis. As long as leukapheresis was not available in our institution, the extreme leukocytosis and eosinophilia required cyto reducer treatment with Hydroxiurea and steroids, in order to prevent the leucostasis and to diminish the toxic tissular effects of eosinophils on heart and lungs (4). The result was encouraging in the beginning; the respiratory distress was alleviated, as well as the skin rash, the back pain and the peripheral edema. The levels of the white blood cells and eosinophils decreased and the number of thrombocytes rose. But the response was of a short duration and a couple of days later the patient status worsened. Taking into account the few reported cases of secondary eosinophilia with good response to either low or standard dose TKI (5-7), a low dose (100-200mg/day) of Glivec was first administered followed by standard dose (400mg/day). No sustained response was attained and soon the patient developed multiple organ dysfunction in parallel with rapid and massive enlargement of the abdominal tumors and died.

The necroptic examination revealed a giant retroperitoneal sarcoma that compressed the left rein and extended in the left psoas muscle as well as multiple secondary tumors in the thoracic and abdominal lymph nodes, pancreas, pleura, lungs and liver with diameters up to 120mm (see FIGURES 8, 9). The histological examination showed myocardial and pulmonary eosinophilic infiltrates. 

CONCLUSION

We rarely see extremely high eosinophilia otherwise than associated with a hematological neoplasm (5). This is the reason why a clinical picture similar to the one presented above first raises the suspicion of such a disease. If the histological examination of involved organs is not available, the diagnosis is based mainly on genetic and molecular assays (8,9) which become more and more important in our days. We have now an entirely new classification of hyper eosinophilic syndromes based on cytogenetic and molecular criteria which gives different perspectives on therapy and prognosis. (3,4,10,11)
REFERENCES


