Myelodysplastic syndrome and pancytopenia responding to treatment of hyperthyroidism: Peripheral blood and bone marrow analysis before and after antihormonal treatment

ABSTRACT
Hematological disorders, especially single lineage abnormalities, have been described in hyperthyroidism. Pancytopenia has been reported, without myelodysplastic syndrome or megaloblastic anemia. We studied the peripheral blood smear and the bone marrow aspiration and biopsy of a 65-year-old lady, who presented with pancytopenia and thyrotoxicosis due to multinodular goiter. She denied ingesting any toxic medication. At diagnosis: WBC: 2500 /ul, platelets count: 58.000/ul, hemoglobin level: 6.5 g/dl. The bone marrow was moderately hyper cellular with moderate myelofibrosis and arrested hematopoiesis. The TSH level was: 0.02 mIU/l (N: 0.25-4), the fT3: 18 pmol/l (N: 4-10), the routine serum immunologic tests were negative. After treatment with single agent neomercazole (carbimazole), complete recovery of the blood cell counts was obtained within one month. The bone marrow aspiration, performed three months after starting therapy, showed normal hematopoiesis. The thyroid function tests returned to normal and no autoimmune reaction was detected on routine serum testing. Persistent response was observed six months later under medical treatment. The patient has refused surgical treatment. Reversible myelodysplastic syndrome may also be part of the changes in blood picture of patients with hyperthyroidism, probably due to direct toxic mechanism.

INTRODUCTION
The myelodysplastic syndrome is a clonal hemopoietic disorder characterized by an abnormal marrow proliferation that merges into acute myelogenous leukemia. It may be associated with prior cytotoxic treatment and recognized as a late complication of chemotherapy particularly with alkylating agent (t-MDS). It may also be secondary to vitamin deficiency or acute toxicity and then it is often reversible.[1,2]

In the myelodysplastic syndrome, anemia is present in over 85% of patients with increased mean corpuscular volume (MCV), neutropenia is present in about 50% of the patients with frequently increased monocytes, thrombocytopenia is present in 25% of the patients, the marrow cellularity is usually normal or increased, the proerythroblasts may be in excess with pathologic sideroblasts, a granulocytic hyperplasia is frequent, megakaryocytes are present and an increase in reticulin and collagen fibers of varying degree is common.

Untreated hyperthyroidism can be associated with anemia (34%), leucocytopenia (5.8%) and thrombocytopenia (3.3%).[1-3] The mechanisms invoked for these single lineage abnormalities were related to the decreased circulating time for some and to the autoimmune reaction for others. Pancytopenia has been rarely reported. All cases were totally reversible as the antithyroid hormonal treatment proceeded. The presence of a myelodysplastic syndrome has not yet been clearly described as a possible consequence of hyperthyroidism.

The observation of a new case of pancytopenia revealing a myelodysplastic syndrome in a patient with hyperthyroidism, which completely resolved under medical treatment led us to review the literature. In gathering information for this article, we systematically searched Pub Med for articles published from 1962 to august 2004.

CASE REPORT
A 65-year-old-woman presented in October 2003 with more than a 10 weeks’ history of weakness, nervousness, back pain, weight loss of 20 kg,
Akoum, et al.: Myelodysplastic syndrome and thyrotoxicosis

Figure 1: A: Pronounced hypercellularity of hematopoietic tissue, resulting in the rarefaction and segregation of fat cells. Hypercellularity involves the three hematopoietic populations, with particularly increased precursors. Absence of atypical cells. (H&E, x50). B: The same slide is seen on higher magnification. The predominance of precursors is confirmed. Mature component, particularly the granulocytes are reduced. Some erythroid nests adhere to bone lamellae. Megakaryocytes are markedly reduced with loss of their sinusoidal orientation. (H&E, x100). C: Silver impregnation x200: Increased meshwork of reticulin fibers. These line vessels wall and ramify around hematopoietic cells. The latter surrounded individually or imprisoned in small nests. This reticulofibrosis is diffuse.

Figure 2: A: Reduction of cellularity with progression to normal. The stromal adipocytes are increased in number and form nests and occasional lobules. (H&E, x50). B: At this magnification, the cellularity is close to normal. Mature cells and precursors are regularly distributed, individually and in small nests. (H&E, x100). C: Silver impregnation x200: Reticulofibrosis is slightly reduced but does not disappear completely.
The fortuitous detection of a pancytopenic myelodysplasia in this 65-year-old lady with thyrotoxicosis led us to consider these two coexisting diseases as two separate entities that are not uncommon at this age group. The unexpected normalization of the hematological disorders under only anti-thyroid treatment of hyperthyroidism and recovered by its treatment.

Because of the unavailability of a cytogenetic laboratory, no further karyotypic analysis was performed in this case to look for 5q and/or 7q deletion seen in approximately 80% of toxic myelodysplastic syndromes and toxic acute myelogenous leukemias (t-MDS / t-AML). The patient denied ingesting any toxic drugs and she never received any cytotoxic chemotherapy or radiotherapy.

The reversible myelodysplastic syndrome has been described[4] separately from the hematological picture of hyperthyroidism. Reversible pancytopenia has been described after successful treatment of hyperthyroidism [Table 1].[5,6,9-12] Thyroid hormones have been known to potentiate erythropoiesis via the ß-adrenergic receptors and reduce the life-span of whole blood component.[5] Immunological mechanisms have also been suggested to be involved in the reduction of the life-span of blood cells and platelets.[9]

The toxicity of thyroid hormones on bone marrow stem cells may be direct or mediated by proteic inhibitory or growth factors. Although the ESR was accelerated suggesting an inflammatory process, all the routine immunologic tests were negative and after normalization of the blood picture it remains accelerated at >60 mm/h.

Shaw and Mehta[6] suggest that thyroid hormones may have a direct effect on hematopoiesis at a stage earlier than erythropoietic stem cell differentiation, disturbing maturation and differentiation of the pluripotent stem cells. Granulopoiesis abnormalities and leukemia have also been described in association with hyperthyroidism and attributed to the direct toxicity of the thyroid hormones.[7,8] In conclusion: Reversible myelodysplastic syndrome may be part of the blood picture changes seen in hyperthyroidism, probably due to direct toxic mechanism.

REFERENCES


Table 1: Reported pancytopenia induced by hyperthyroidism and recovered by its treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Bone marrow</th>
<th>Peripheral blood</th>
<th>Treatment of hyperthyroidism</th>
<th>Cause of hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Iguchi</td>
<td>F</td>
<td>51</td>
<td>Hyperplastic</td>
<td>Pancytopenia</td>
<td>Carbimazole</td>
<td>Graves'</td>
</tr>
<tr>
<td>1995</td>
<td>Duquenne</td>
<td>F</td>
<td>72</td>
<td>Dysgranulopoiesis (9% eosinophilia)</td>
<td>Pancytopenia</td>
<td>Methimazole</td>
<td>Adenoma</td>
</tr>
<tr>
<td>1995</td>
<td>Duquenne</td>
<td>F</td>
<td>66</td>
<td>Hypoplastic</td>
<td>Pancytopenia</td>
<td>Carbimazole</td>
<td>Graves'</td>
</tr>
<tr>
<td>1995</td>
<td>Duquenne</td>
<td>F</td>
<td>83</td>
<td>Normal</td>
<td>Pancytopenia</td>
<td>Carbimazole</td>
<td>Graves'</td>
</tr>
<tr>
<td>1998</td>
<td>Bertola</td>
<td>F</td>
<td>63</td>
<td>Slight dyserythropoiesis</td>
<td>Pancytopenia</td>
<td>Carbimazole</td>
<td>Graves'</td>
</tr>
<tr>
<td>2000</td>
<td>Masuoka</td>
<td>F</td>
<td>45</td>
<td>Normal</td>
<td>Pancytopenia</td>
<td>Carbimazole</td>
<td>Graves'</td>
</tr>
<tr>
<td>2001</td>
<td>Soeki</td>
<td>M</td>
<td>49</td>
<td>Hyperplastic (Arrested hematopoiesis)</td>
<td>Pancytopenia</td>
<td>Carbimazole</td>
<td>Graves'</td>
</tr>
<tr>
<td>2002</td>
<td>Shaw</td>
<td>M</td>
<td>46</td>
<td>Normal (Post-transplant)</td>
<td>Pancytopenia</td>
<td>Carbimazole</td>
<td>Graves'</td>
</tr>
</tbody>
</table>

Palpitations, pallor, low grade fever (38° - 38.5°C), fine tremor and excessive perspiration. She had no evidence of focal or general infection. She was noted to have an enlarged neck with a very large multinodular goiter. Complete work-up including isotopic bone scan, lumbar and dorsal CT scan and routine X-rays showed only severe osteopenia. CT scan of the neck, the thorax and the abdomen showed a huge multinodular goiter extending into the retrosternal area. The electrocardiogram showed a supraventricular tachyarrhythmia. Thyroid function tests revealed a TSH level of 0.02 mIU/l (N: 0.25-4) and an T3 level of 18 pmol/l (N: 4-10). The diagnosis of hyperthyroidism was made.

A blood count at diagnosis showed the white blood cells at 2500 /μl and the platelets at 58.000/μl. The hemoglobin level was 6.5 g/dl, the MCV was 88 fl. The sedimentation rate ESR was 115 mm/h.

To explain the pancytopenia, a bone marrow aspiration and biopsy were performed: a moderately hypercellular marrow with moderate myelofibrosis and arrested hematopoiesis was noted.

The patient was started on an antithyroid agent, carbimazole: 30 mg tid. A marked improvement in the clinical picture was seen within one month and the thyroid function returned to normal. The peripheral blood counts became normal one month later and the bone marrow analysis performed four months later showed normal hematopoiesis with no evidence of myelodysplasia [Figures 1 and 2]. A persistent response was observed six months later under medical treatment. The patient refused surgical treatment.

DISCUSSION

The fortuitous detection of a pancytopenic myelodysplasia in this 65-year-old lady with thyrotoxicosis led us to consider these two coexisting diseases as two separate entities that are not uncommon at this age group. The unexpected normalization of the hematological disorders under only anti-thyroid hormonal treatment is an uncommon event since the natural history of almost all primary myelodysplastic syndromes is to progress into acute myelogenous leukemia.[1,2]


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