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Erythrocytosis in a patient with chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) can be accompanied by compensatory secondary erythrocytosis. However, the exact prevalence of secondary erythrocytosis in COPD is unknown. Although diagnostic criteria for polycythemia vera versus secondary erythrocytosis are mutually exclusive, we describe here the coexistence of polycythemia vera and COPD in the same patient.

Key words: secondary polycythemia, chronic myeloproliferative disorders, polycythemia vera, COPD, differential diagnosis

Polycythemia is a rather common finding in clinical practice. The distinction between polycythemia vera (PV) and secondary polycythemias (SP) is crucial both for prognosis and treatment. Flowcharts have been developed and standardized, which enables the clinician to distinguish between these two entities.[1]

Chronic obstructive pulmonary disease (COPD) can be accompanied by compensatory SP.[2] However, the exact prevalence of SP in COPD is unknown. Although diagnostic criteria for PV versus SP are mutually exclusive, we describe here the coexistence of PV and COPD in the same patient.

Case Report

A 67-year-old man (G.B.) was hospitalized because of fever, productive cough, and worsening dyspnea. The first evaluation showed an agitated, obese man in respiratory distress with fever (38°C), orthopnea, tachypnea (25 breaths/min) and marked cyanosis. There were mild ankle edema, jugular venous distension and digital clubbing. Physical examination of the thorax showed signs of chronic emphysema, mild wheezing, a left pleural friction rub and bibasilar inspiratory rales. There were also splenomegaly and mild hepatomegaly. The remaining physical examination was unremarkable. Arterial blood gases (evaluated while the patient was breathing room air) were as follows: pCO_2: 63 mmHg; pO_2: 37 mmHg; sO_2: 65%; pH: 7.37. Laboratory tests showed erythrocytosis (RBC: 6.21×10^{12}/L; Hb: 18.3 g/dL; Hct: 0.61) and mild thrombocytosis (458×10^9/L). Normal ranges for men with the electronic counter Coulter S-Plus IV are the following: RBC = 4.52-5.9$\times10^{12}$/L; Hb = 14-17.5 g/dL; Hct = 0.42-0.50; plt = 130-400$\times10^9$/L. The red cell indices, white cell number, differential count and peripheral blood cell morphology were normal. Serum LDH was 590 mU/mL (normal range = 200-460 mU/mL). The other routine laboratory tests were within the normal range. Chest X-ray showed bilateral fibrothorax, pulmonary emphysema, congestion of the pulmonary vasculature and a right-sided pleural effusion (Figure 1a). In a latero-lateral view (not shown) a right retrocardiac inflammatory infiltrate was present. The patient was a retired policeman. He had smoked about 40 cigarettes a day since the age of 25, having quitted at the age of 61 for respiratory problems. He also admitted habitual abundant food and alcohol intake. At the age of 21, he was treated with therapeutic pneumothorax for tuberculosis. At the age of 40, chronic bronchitis was diagnosed. In the following years, he was found to be polycythemic (Hb: 18-19 g/dL) and regularly donated blood till the age of 56. In the last four years the patient experienced worsening dyspnea and noticed swollen feet.

At a first glance, this clinical presentation does not pose particular problems. In a patient with COPD, fibrothorax and myocardial insufficency, a lower airway infection worsened a pre-existing respiratory failure. The erythrocytosis and the thrombocytosis are easily attributable to the chronic respiratory insufficency and to the acute infection, respectively. Excessive alcohol intake and cardiac failure could account for the hepato-splenomegaly.

In the hospital, the patient was treated with oxygen by mask, i.v. furosemide, theophylline, ceftazidime and underwent 5 phlebotomies for a total of 1,500 mL of blood. After a few days, the fever had disappeared and the signs of cardiac and respiratory insufficency were improved. Arterial blood gases (in room air) were as follows: pCO_2: 45 mmHg; pO_2: 61 mmHg; sO_2: 86%; pH: 7.40. Laboratory tests showed a reduction of plasma Hb

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to 16.1 g/dL and Hct to 0.55, increased plasma LDH (1040 mU/mL) and were otherwise unchanged. The platelet count was only slightly increased (471×10^9/L).

Spirometric tests yielded the following results:
- FVC: 3.89 L (94% of predicted value);
- FEV1/VC: 75% (62% of predicted value);
- RV: 3.17 L (123% of predicted value);
- DLCO: 4.3 mmol/KPa.min (46% of predicted value).

These data demonstrated a conspicuous impairment of both ventilation (obstructive type) and alveolar gas diffusion.

An ultrasound scan of the upper abdomen showed that the liver was within the normal limits for size and echostructure, and confirmed the presence of splenomegaly (vertical diameter 230 mm). No signs of portal hypertension were detected.

Despite the clear evidence of COPD with SP, we suspected the patient might be affected by a chronic myeloproliferative disorder. Clues for this suspicion were the presence of splenomegaly, the increasing levels of serum LDH, the persistence of thrombocytosis, and the lower than expected decrease of Hb and Hct after repeated phlebotomies. It should be noted that frequently splenomegaly, due to a sequestering effect, lowers the blood cell count. We were conscious that these facts were a fragile support to the diagnosis of a myeloproliferative syndrome, being realistically attributable to the recent acute infection, chronic alcoholic liver disease and cigarette smoking.

The patient underwent the following investigations:
- bone marrow aspirate: dry tap after 4 attempts.
- bone marrow biopsy: the bone marrow was hypercellular, with a cell/fat ratio of 5:1. Myeloerythroid ratio was 3:1. The erythroid lineage was slightly increased, with normal maturation. The most striking feature was a marked increase of the megakaryocytes, often clustered in groups of 10-15 elements. Among these, a great variability of shapes and sizes was present, together with a significant amount of micromegakaryocytes (Figure 1b). A slight increase in the reticulin network was observed with specific stain (Figure 2a);
- cytogenetics on peripheral blood leukocytes: no mitoses were observable;
- leukocyte alkaline phosphatase (LAP) score: 42 (normal range: 25-100);
- serum vitamin B_{12}: 1163 pg/mL (normal range 200-900);
- serum erythropoietin (EPO): < 0.5 mU/mL on two separate determinations (normal range: 10-18);
- circulating erythrocyte mass: 48 mL/kg (normal value for men: ≤ 36).

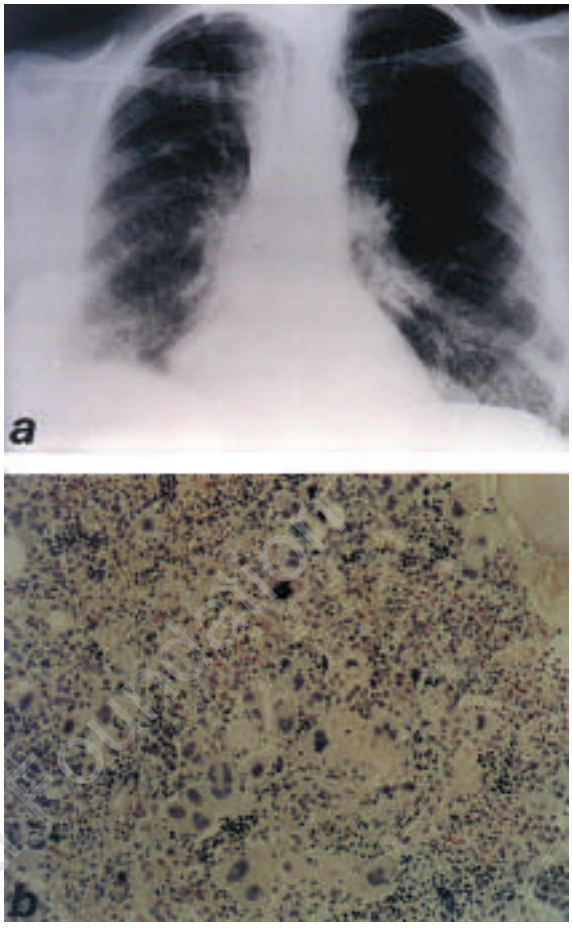

Figure 1.
a: patient's chest X-ray (frontal view) shows bilateral fibrothorax, pulmonary emphysema, congestion of the pulmonary vasculature and a right-sided pleural effusion; b: bone marrow biopsy at diagnosis shows trilineage hyperplasia, more pronounced in the megakaryocyte lineage, with medium degree atypia (hematoxylin-eosin, original magnification 100×).

Now the clinical scenario is markedly changed. The bone marrow morphology is diagnostic for a chronic myeloproliferative disorder, and the other ancillary tests, besides excluding pseudoerythrocytosis, are in line with this interpretation. Considering the differential diagnosis of chronic myeloproliferative disorders, chronic myelogenous leukemia (CML) is obviously ruled out.[3] The diagnosis of essential thrombocythemia has as a prerequisite the presence of a sustained thrombocytosis, not less than 600×10^9/L.[4] The two major diagnostic options in the present case are idiopathic myelofibrosis (IM) and PV. Both frequently exhibit a slight thrombocytosis, the main differential feature being an increase in the red blood cell mass in the latter. However, IM has a typical peripheral blood picture with dacryocytes,

erythroblasts and frequently immature granulocytes, and the bone marrow usually shows collagen fibrosis instead of a mere increase of reticulin fibers.[5] It should be noted that a normal LAP score, as our patient had, is strong evidence against the diagnosis of CML, but not of PV, being observable in a minority of patients.[6]

A diagnosis of polycythemia vera with cardiac and respiratory insufficiency was made, and the patient was discharged with a program of ambulatory follow-up. Chemotherapy with hydroxyurea was scheduled in the probable evenience that additional phlebotomies would be insufficient to control the disease. The patient neglected medical care.

He showed up again about a year and a half afterward, complaining of marked anorexia, astenia and weight loss. Physical evaluation showed increased splenomegaly, while his cardiorespiratory condition was stable. Hemocytometry showed pancytopenia: Hb 8 g/dL; WBC $1,500\times10^6$/L with a normal differential, platelets 112×10^9/L. Bone marrow biopsy showed a conspicuous reduction of the cellularity together with a marked increase in fibrosis (Figure 2b). The patient was lost to follow-up again and died in another hospital a few weeks afterwards of overwhelming pneumonia.

Bone marrow insufficiency caused by progressive reticulin fibrosis is the most frequent final step in the natural history of PV.[7]

A few adjunctive distinctive features in a rather linear clinical presentation, i.e. a patient affected by acute broncopulmonary infection complicating COPD, induced us to look for and demonstrate the coexistence of a chronic myeloproliferative disorder and COPD. Among the chronic myeloproliferative disorders, PV seemed to represent the best diagnostic option. Nevertheless, we had to confront a major obstacle. In 1975 the Polycythemia Vera Study Group (PVSG) proposed a set of simple diagnostic criteria for PV, whose main objective was to avoid the inclusion in study protocols of patients with SP.[1] According to the PVSG guidelines, PV can be diagnosed in a patient when an increase in the red cell mass and a normal arterial oxygen saturation are present, together with splenomegaly or two of the following minor criteria: thrombocytosis, leukocytosis, markedly elevated leukocyte alkaline phosphatase, increased serum vitamin B_{12}. The role of serum vitamin B_{12} concentration as a minor diagnostic criterium for PV has been recently questioned.[8] The PVSG criteria have been widely accepted in the scientific community , with more than 270 citations in the Science Citation Index[9] and adopted almost universally also in clinical practice. In particular, according to these criteria, no polycythemic patient whose arterial oxygen saturation is less than 92% can be considered to have PV. The present patient had two major (an increased red cell mass and splenomegaly) and one minor diagnostic criteria (thrombocytosis), but had a low arterial oxygen saturation due to chronic respiratory insufficency.

*A few years ago, in his comments on the differential diagnosis of polycythemia, Ernest Beutler stated that "*It is not the red cell mass that is helpful in leading one to the diagnosis of secondary polycythemia but rather the absence of leukocytosis, thrombocytosis and splenomegaly*".[10] We believe that in this case PV is not merely the best diagnosis among the chronic myeloproliferative syndromes, but is undoubtedly distinguished from SP by the undetectable levels of serum EPO found in our patient. Serum EPO was not included in the original PVSG criteria, presumably because of the overlap between patients and controls in the lower range of the values, due to methodological problems. With more accurate laboratory techniques, serum EPO has been recently demonstrated to be a very sensitive marker, capable of accurately discriminating between PV and SP.[11-13] Due to the high prevalence of COPD the coexistence of PV and SP in the same patient*

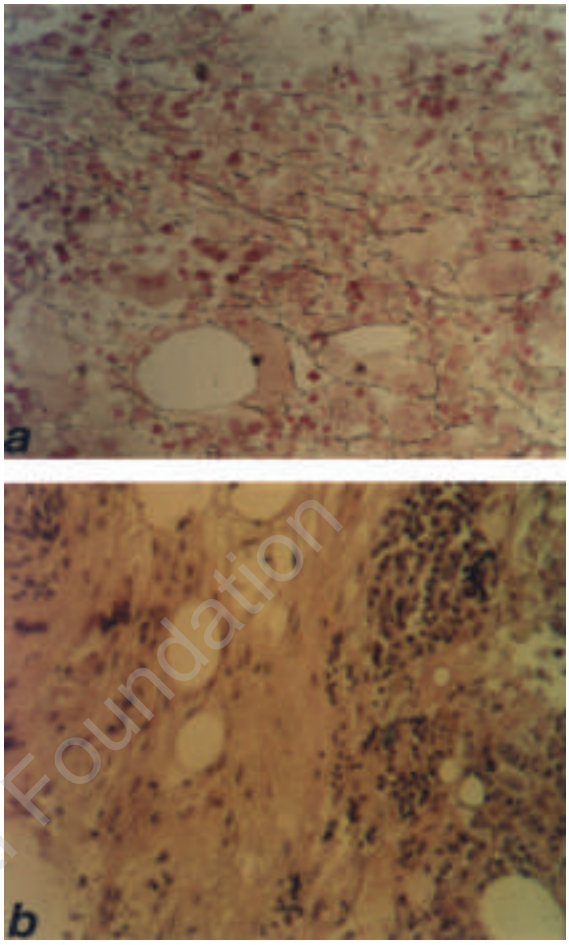

Figure 2.
a: bone marrow biopsy at diagnosis shows an increase in reticulin fibers, particularly evident around megakaryocytes (Gomori's silver impregnation, original magnification 250×).
b: bone marrow biopsy after 18 months shows extensive collagenization and a marked decrease of cellularity (hematoxylin-eosin, original magnification 100×).

is not an improbable event;[2] such patients could be missed to diagnosis if the stringent PVSG criteria are acritically adopted. Did our patient really have SP with superimposed PV, or did he simply have misdiagnosed PV? About fifteen years had passed between the first discovery of polycythemia and the patient's hospitalization, and this interval is similar to the median duration of survival in large groups of PV patients.[14,15]

In conclusion, we would like to propose that, although the occurrence of PV in COPD is potentially rare, care should be taken to single out these patients in order to offer them proper care and counselling. Serum EPO determination might help in the initial identification of PV in COPD patients in whom suspicion is justified by laboratory and clinical findings.

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