Case Report / Caso Clinico

JAK2 V617F mutation negative erythrocytosis (or how to more simply perform diagnosis and treat a patient with increased hematocrit)

Eritrocitosi in assenza di mutazione JAK2 V617F (o come effettuare più semplicemente diagnosi e trattamento di un paziente con ematocrito elevato)

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SUMMARY
This case report focuses on a 71-year old patient affected by unknown dyspnea and erythrocytosis referred by his general practitioner to our center for specialist advice after a hematological examination had excluded polycythemia vera on grounds of negative test for JAK2 V617F / exon 12 mutation. An accurate clinical history and physical examination accompanied by respiratory function tests resulted in diagnosis of JAK2 V617F mutation negative erythrocytosis, and treatment could be started. The discussion examines decisional algorithms when a polyglobulic patient is referred for diagnosis.

Keywords: Dyspnea, erythrocytosis, JAK2 V617F, polycythemia, pulmonary function tests.

RIASSUNTO
Questo caso report si riferisce ad un paziente di 71 anni, inviato dal suo medico di medicina generale alla nostra osservazione per dispnea di natura da determinare ed eritrocitosi, dopo essere stato sottoposto a consulenza ematologica ed avere escluso la presenza di policitemia vera con riscontro di test negativo per mutazione gene JAK2 V617F / esone12. Un’attenta valutazione della storia clinica ed un accurato esa-me obiettivo, insieme a semplici test di funzionalità respiratoria, avrebbero consentito una rapida diagnosi permettendo l’inizio di una terapia adeguata. Vengono discussi gli algoritmi decisionali applicabili ai pazienti poliglobulici.

Parole chiave: Dispnea, eritrocitosi, JAK2 V617F, policitemia, test di funzionalità polmonare.

CLINICAL CASE
A 71-year old patient, male, former shepherd and farmer with seasonal periods spent at high altitude (3000 m), ex-smoker (60 pack/years), was referred by his general practitioner to our center for specialist consultation after being referred for a hematological visit because of erythrocytosis. The hematological examination excluded the diagnosis of polycythemia vera after a negative test for JAK2 V617F / 12 exon mutation.

Medical history: A liver hydatic cyst was removed in 1984. Hypertension was treated from 1998.
Cerebrovascular disease with two strokes and consequent left partial hemiparesis occurred in 2006 and 2008. The patient was treated with beta blocker (atenolol 100 mg), angiotensin receptor blocker and thiazide diuretic (irbesartan 300 mg, hydrochlorothiazide 12.5 mg); dyslipidemia was treated with hypolipidemic drugs (atorvastatin 20 mg); he was on therapy with anticoagulants (warfarin 5 mg) according to the international normalized ratio (INR). A test for the JAK2 V617F / 12 exon mutation was performed, with negative result, after an incidental finding of erythrocytosis (Hb 19.8 mg/dL, hematocrit 58.8%, RBC 6.9 x 10^6) after the patient had been living at high altitude (about 3000 meters). Chest x-ray and chest CT scan documented subsegmental dysventilation areas in the posterior part of the lower left lobe with no expansive lesions or lymphadenopathies with lifting of left hemidiaphragm (signalled in previous chest x-ray in 2008). Snoring without referred sleep apnea was reported. Abdominal ultrasonography showed enlarged liver with cololithiasis. **Physical examination:** height 1.62 m, weight 76 Kg, body mass index 28.9 kg/m². Pulsoximetry 91% (ambient air). Pulse rate: 62 rhythmic; blood pressure: 140/95 mm Hg; thoracic examination: symmetrical hemithorax, slightly sour vesicular murmur spread over all lung fields, reduced at the left base. Reduced motility of left hemidiaphragm. Cardiac examination: valid rhythmic heart sounds, apparently free of pauses. Abdominal examination: tractable abdomen, painless, hypochondriac organs within the limits. No lower limb edema. Neurological examination: outcomes of left hemiparesis. At this time (Figure 1) a complete respiratory function study, blood gas analysis and nocturnal (8 channels) cardiopulmonary monitoring were scheduled. **Pulmonary function tests** (Figure 2) revealed: “mild restrictive alteration without bronchial obstruction.

**FIGURE 1: ALGORITHM FOR SUSPECTED ERYTHROCYTOSIS WHEN LEUKOCYTOSIS, THROMBOCYTOSIS, OR SPLENOMEGALY IS NOT PRESENT**

![Algorithm](image)

**FIGURE 2: TYPICAL PULMONARY FUNCTION TESTS**

![Pulmonary Function Tests](image)
Mild alteration of lung diffusion test for carbon monoxide (DLCO) after correction for reduced lung volumes. Regular ventilatory pattern. Normal occlusion pressure (P100). Reduced maximal inspiratory flow (FEF 25%) and peak expiratory flow (PEF).

Definition of abbreviations: Chg, change; ERV, expiratory reserve volume; FEF, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FET, forced expiratory time; FIF, forced inspiratory flow; FRC PL, functional residual capacity measured with plethysmograph; FVC, forced vital capacity; IC, inspiratory capacity; Meas, measured; PEF, peak expiratory flow; PEFT, peak expiratory flow time; Ref, reference value; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

FIGURE 2: SPIROMETRY AND PLETHYSMOGRAPHIC LUNG VOLUMES IN THE STUDIED PATIENT

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Pre Meas</th>
<th>Ref</th>
<th>% Chg</th>
<th>Post Meas</th>
<th>% Chg</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC Liters</td>
<td>3.15</td>
<td>1.00</td>
<td>2.14</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>FEV1 Liters</td>
<td>2.42</td>
<td>0.84</td>
<td>1.62</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>74</td>
<td>12</td>
<td>76</td>
<td></td>
<td></td>
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<tr>
<td>FEV1/SVC %</td>
<td>75</td>
<td></td>
<td></td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>FEF25% L/sec</td>
<td>1.04</td>
<td>1.28</td>
<td>0.48</td>
<td>46</td>
<td></td>
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<tr>
<td>FEF50% L/sec</td>
<td>7.04</td>
<td>1.99</td>
<td>4.19</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>FEF75% L/sec</td>
<td></td>
<td></td>
<td>1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FET100% Sec</td>
<td>5.60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEFT Sec</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Plethysmography</th>
<th>Pre Meas</th>
<th>Ref</th>
<th>% Chg</th>
<th>Post Meas</th>
<th>% Chg</th>
</tr>
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<tbody>
<tr>
<td>VC Liters</td>
<td>3.24</td>
<td>0.92</td>
<td>2.14</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>FRC PL Liters</td>
<td>3.34</td>
<td>0.99</td>
<td>2.20</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>RV Liters</td>
<td>2.45</td>
<td>0.67</td>
<td>2.02</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>ERV Liters</td>
<td>0.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC Liters</td>
<td>5.86</td>
<td>1.15</td>
<td>4.16</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>RV/TLC %</td>
<td>42</td>
<td>9</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC Liters</td>
<td>1.59</td>
<td></td>
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</tr>
</tbody>
</table>

FIGURE 3: RESPIRATORY EVENTS POLYSOMNOGRAPHIC ANALYSIS AND OXYHEMOGLOBIN VALUES DURING THE NOCTURNAL RECORDING

RESPIRATORY EVENTS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Obstructive</th>
<th>Central</th>
<th>Mixed</th>
<th>All apneas</th>
<th>Hypopnea</th>
<th>All events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>25</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Per hour</td>
<td>3.6</td>
<td>0.0</td>
<td>0.0</td>
<td>3.6</td>
<td>0.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Mean duration (mm:ss)</td>
<td>0:17</td>
<td>0:000</td>
<td>0:000</td>
<td>0:17</td>
<td>0:25</td>
<td>0:18</td>
</tr>
<tr>
<td>Maximum duration (mm:ss)</td>
<td>0.35 (23:22:53)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.35 (23:22:53)</td>
<td>0.28 (22:31:07)</td>
<td>0.35 (23:22:53)</td>
</tr>
<tr>
<td>Apnea Hypopnea Index (AHI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.9</td>
<td></td>
</tr>
</tbody>
</table>
Blood gas analysis showed PaO₂ 52.7 mm Hg; PaCO₂ 45.9 mm Hg; pH 7.40; oxyhemoglobin saturation 85.9%; carboxyhemoglobin 2.1%; methemoglobin 1%; P50 (partial pressure of oxygen at which 50% of hemoglobin is saturated with oxygen) 24.9 mm Hg.

Nocturnal (8 channels) cardiopulmonary monitoring (Figure 3) showed low apnea-hypopnea index (AHI: 3.9 events/hour) with low mean nocturnal hemoglobin saturation (86%) and 65% of the night spent with values below 90%.

A 6-minute walking test (Figure 4) showed 275 meters walking distance with slight desaturation below 90% at the beginning of the test.

DIAGNOSIS

Dyspnea and erythrocytosis secondary to hypoxemia in restrictive lung disease.

TREATMENT

The patient started oxygen therapy 1.5 L/min by nasal cannula in the night. Blood gas analysis showed no increased levels of carbon dioxide during oxygen therapy and a nocturnal cardiopulmonary monitoring showed reduction of time spent with SpO₂ < 90% from 69% to 13%. Oxygen was then increased to 2 L/min. After 2 months hematocrit was reduced to 51% and hemoglobin was reduced to 17 g/dL.

DISCUSSION

Traditionally, polycythemia has been used to identify a group of several disorders with an increase in circulating red cells and persistently raised hematocrit (Hct) [1]. Since only the red cell lineage is involved, in this article we have chosen to use throughout the term erythrocytosis. Polycythemia is intended in relation to the clonal disorder, polycythemia vera (PV), in which three cell lineages are involved. In practice it is useful to classify erythrocytosis as being congenital or acquired [2,3] (Table I).

TABLE I: CLASSIFICATION OF ERYTHROCYTOSIS

1. Congenital erythrocytosis
   a. Associated with reduced P50 (partial pressure of oxygen at which 50% of hemoglobin is saturated with oxygen)
      i. High-oxygen-affinity hemoglobinopathy
      ii. 2,3-bisphosphoglycerate
      iii. Methemoglobinemia
   b. Associated with normal P50
      i. VHL gene mutations including Chuvash
      ii. Erythropoietin receptor mutations

2. Acquired erythrocytosis
   a. Clonal (polycythemia vera)
   b. Secondary
      i. Hypoxia driven
         1. Chronic lung disease
         2. Right-to-left cardiopulmonary shunts
         3. High-altitude habitat
         4. Tobacco use/carbon monoxide poisoning
         5. Sleep apnea/hypoventilation syndrome
         6. Renal artery stenosis
      ii. Hypoxia independent
         1. Use of androgen preparations/erythropoietin injection
         2. Post-renal transplant
         3. Cerebellar hemangioblastoma/meningioma
         4. Pheochromocytoma/uterine leiomyoma/renal cysts/parathyroid adenoma
         5. Hepatocellular carcinoma/renal cell carcinoma

only analysis that defines the predominant type of marrow biopsy is therefore important, as it is the matter of this manuscript. 

CONCLUSIONS

In our case, an accurate anamnestic and careful objective examination (erythrocytosis, low hemoglobin saturation, hypoxemia and hypomobility of the left hemidiaphragm) could have led immediately to a clinical diagnosis of secondary erythrocytosis and would have avoided the implementation of further tests such as analysis of JAK2 V617F / exon 2 mutation with delay in the diagnosis and treatment.

CONFLICT OF INTEREST STATEMENT: None of the authors has any conflict of interest to declare in relation to the subject matter of this manuscript.

References


