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Caso clinico

An unusual case of secondary pure red cell aplasia (PRCA) that occults a squamous carcinoma of the tongue

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Abstract

We report a case of acquired pure red cell aplasia (APRCA) associated with carcinoma of the tongue: the first was considered a rare paraneoplastic syndrome. We point out that there is no case in literature with this association.
After surgical operation (subglottic laryngectomy + right lymphadenectomy + laterocervical on the right) the transfusions required, at the beginning very frequent, decreased relevantly. This is a typical case where the paraneoplastic syndrome precedes the diagnosis of the primary carcinoma of the tongue (one year before what happens in bronchogenic carcinoma).

Keywords: pure red cell aplasia, paraneoplastic syndrome, carcinoma of the tongue
Un raro caso di aplasia eritroide pura che occulta un carcinoma squamoso della lingua
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INTRODUCTION

Pure red cell aplasia (PRCA) describes a condition where the RBC precursors in bone marrow are nearly absent, while megakaryocytes and WBC precursors are usually present at normal levels. In 1922, this condition was recognised by Kaznelson [1] as a different entity from aplastic anaemia. Pure red cell aplasia exists in several forms, and the most common one is an acute self-limited condition.

Acquired pure red cell aplasia is chronic and is often associated with underlying disorders like thymomas [2], lymphomas [3], and autoimmune diseases. Initially a congenital form of pure red cell aplasia was described by Joseph in 1936 and by Diamond-Blackfan in 1938 [4]. Congenital pure red cell aplasia is a lifelong disorder, and it is associated with physical abnormalities. Both acquired and congenital pure red cell aplasia are occasionally refractory to therapy (Table I).

CASE REPORT

A 70-year-old teacher, a good eater, didn't drink any wine and any alcoholic drinks. His intestinal transit and his diuresis were normal. He was a nonsmoker, a single and he didn't take any therapy.

In his past medical history we found hypertension, prostatic hypertrophy, appendectomy, and melanoma in the left arm in 2002. In November 2008 he was admitted to Hospital because of wheezing with fever chills, symmetrical arthralgias, and relevant asthenia. He was apiretic. Physical examination revealed obtuseness chest and showed mean pleural effusion; the neurological examination showed that the patient was sound; the cranial nerve function was observed: the sensation, the muscle strength, and tenden reflex were normal.

The heart sound was normal, and there were no oedema on lower extremities. In the abdomen we found no specific abnormalities and Blumberg sign was negative. There were

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"Congenital" form (Diamond-Blackfan anaemia)
Acquired PRCA
Parvovirus B19 infection
- Transient aplastic crisis (TAC) in patients with shortened erythrocyte life span
- Chronic type of bone marrow failure in immunosuppressed patients

Immunological suppression of erythropoiesis
- Antibody mediated
  - Antibody against red-cell progenitors
    - Transient erythroblastopenia in childhood (TEC)
    - Adult form
    - ABO-incompatibility following bone marrow transplantation
  - Antibody against erythropoietin

αβ or γδ T cell-mediated
- T-helper cell-mediated antibody production
- MHC-restricted, recognition of red-cell progenitors
- MHC-unrestricted recognition of red-cell progenitors

NK cell- or T cell-mediated
- MHC-unrestricted cytotoxicity

Associated with pregnancy
Associated with certain drugs and toxins
Initial manifestation of a pre-leukaemic syndrome

Table I
Types of pure red cell aplasia. Modified from [5]

no skin lesions, the genitals were normal, and we found no rash and no lymphadenopathy. He was overweight.

The blood tests revealed the results shown in Table II.

Tuberculin skin testing (Mantoux test) and a single smear-sputum sample for *Mycobatterium tuberculosis* were negative. The urinalysis and proteinuria were normal. The testing stool for the presence of haemoglobin was negative. The electrocardiogram (ECG) showed a normal rhythm at a rate of 87 bpm. The cystoscopy explored prostate lobes, finding mucosal hyperaemia bleeding heavily at the passage of the instrument. The bladder mucosa was regular.

The neck/thoracic Magnetic Resonance Imaging (MRI) detected a pleural effusion on the left. The MRI performed on the abdomen showed gallbladder-renal calculi and prostatic hypertrophy. The chest CT confirmed the gallbladder calculi and the abundant pleural effusion on the left, adding the detection of not dependent focal lesions of the remaining lung parenchyma. The tracheal and bronchial branches were normal, such as adrenal glands. The PET was negative.

A thoracentesis was performed for pleural effusions: the ratio of pleural fluid to serum protein resulted greater than 0.5. The ratio of pleural fluid to serum lactate dehydrogenase (LDH) was greater than 0.6. Pleural fluid LDH is greater than two thirds of the upper limits of normal serum value (protein = 3.9 g/dl) [6]. For this test, in accordance with the criteria proposed by Light, this pleural effusion was considered an exudate [6]. Culture of infected pleural fluid yielded negative results.

The echocardiography presented minimal pericardial effusion.

The haematic tests revealed lymphocytes = 55% and neutrophils = 42%. Cytology findings were negative for neoplastic cells.

Because of the negativity of the clinical examinations during hospitalisation, the patient was transferred to the Thoracic Surgery, where he was subjected to pleural biopsy: the pathologic specimen showed a chronic pleuritis. During hospitalisation ticarcillin 4.5 mg × 3, prednisone 50 mg/die, and a gastroprotective drug were administered. The patient was discharged after 20 days with good resolution of the general clinical condition and an outpatient follow-up was arranged. At home the patient continued steroid treatment since there was the suspect of a possible form of autoimmune disease (maybe systemic lupus erythematosus). This suspicion roused by the results of the following tests: positive antibody and native DNA, pleural effusion, and pericardial effusion associated with moderate megaloblastic anaemia, which was already present since some time.

In March 2009 he was re-hospitalised in Department of Internal Medicine for severe megaloblastic anaemia (Hb = 5.8 g/dl;

platelets = 150,000/mm^3; MCV = 110 fl), dyspnoea, and tachycardia.

The gastroscopy performed showed chronic gastritis, while the colonscopy was normal.

A computed tomographic scanned neck, chest, abdomen with administration of contrast material: the main pulmonary artery and the pulmonary arterial vasculature were normal, such as the lung parenchymal.

The biopsy of the bone marrow revealed a 20% cellularity (hypocellular) and a normal myeloid series. The erythroid series was aplastic, while the megakaryocytic one resulted hyperplastic. We found also interstitial infiltrates of lymphocytes for 25% of elements with immunophenotype CD3-CD20 positive (reactive lymphocytes), and CD34 cells 2%. The test for the PNH (Paroxysmal Nocturnal Haemoglobinuria)

Parameter	Results	Normal range
WBC	4,990/mm^3	4,500-11,000/mm^3
Neutrophils	40%	-
Lymphocytes	55%	-
Plts	150,000/mm^3	150,000-350,000/mm^3
Hb	10.5 g/dl	14-18 g/dl
MCV	110 fl	80-100 fl
ESR	31 mm/hour	2-10 mm/hour
INR	1.1	0.8-1.2
Fibrinogen	278 mg/dl	175-400 mg/dl
Glucose	97 mg/dl	70-110 mg/dl
Urea	37 mg/dl	10-50 mg/dl
Creatinine	1 mg/dl	0-1.5 mg/dl
Total cholesterol	112 mg/dl	< 200 mg/dl
TAG	142 mg/dl	40-170 mg/dl
Total bilirubin	0.8 mg/dl	< 1 mg/dl
Uric acid	5.7 mg/dl	3.6-8.5 mg/dl
Ferritin	226 ng/dl	30-300 ng/dl
Na^+	146 mEq/l	135-145 mEq/l
K^+	4.4 mEq/l	3.4-4.8 mEq/l
GOT	25 U/l	9-25 U/l
GPT	24 U/l	7-30 U/l
GGT	37 U/l	7-33 U/l
ALP	50 U/l	40-115 U/l
LDH	493 U/l	110-210 U/l
PT	5.8 sec	11-16 sec
Amylase	42 U/l	10-220 U/l
Lipase	30 U/l	114-286 U/l
Alpha fetoprotein	1.38 ng/ml	< 10 ng/ml
CEA	1.6 ng/ml	< 5 ng/ml
Ca 19-9	30 U/ml	0-40 U/ml
CRP	0.3 mg/l	< 8 mg/l
ACE	7 nmol/ml	8-22 nmol/ml
Vitamin B12	675 µg/dl	200-900 µg/dl
Folic acid	13 ng/ml	3.1-17.5 ng/ml
HIV	Negative	-
HBV	Negative	-
HCV	Negative	-
ANA	1:640	-
ENA	Negative	-
LAC	Negative	-
ACA	Negative	-
B2GP1	Negative	-
Anti-dsDNA	Positive	-
C3	In range	
C4	In range	
Rheumatoid factor	In range	
Antibodies CCP	In range	

Table II

Results of the blood tests performed

ACA = Anti-Cardiolipin Antibody;
ACE = Angiotensin Converting Enzyme;
ALP = ALkaline Phosphatase;
ANA = ANtinuclear Antibody;
Antibodies CCP = antibodies anti-citrulline;
B2GP1 = Beta 2 GlycoProtein 1 Antibody;
C3 = C3 complement component;
C4 = C4 complement component;
Ca 19-9 = Carbohydrate antigen 19-9;
CEA = CarcinoEmbryonic Antigen;
CRP = C Reactive Protein;
dsDNA = double-stranded DNA;
ENA = anti-Extractable Nuclear Antigens;
ESR = Erythrocyte Sedimentation Rate;
GGT = Gamma-Glutamyl Transferase;
GOT = Glutamic Oxaloacetic Transaminase;
GPT = Glutamic Pyruvic Transaminase;
HBV = Hepatitis B Virus;
HCV = Hepatitis C Virus;
HIV = Human Immunodeficiency Virus;
INR = International Normalized Ratio;
LAC = Lupus AntiCoagulant antibody;
LDH = Lactate DeHydrogenase;
MCV = Mean Corpuscular Volume;
PT = Prothrombin Time;
TAG = TriAcylGlycerol

Serositis	Pleurisy, pericarditis on examination or diagnostic ECG or imaging
Oral ulcers	Oral or nasopharyngeal, usually painless; palate is most specific
Arthritis	Nonerosive, two or more peripheral joints with tenderness or swelling
Photosensitivity	Unusual skin reaction to light exposure
Blood disorders	Leukopenia (< 4 × 10^3 cells/µl on more than one occasion), lymphopenia (< 1,500 cells/µl on more than one occasion), thrombocytopenia (< 100 × 10^3 cells/µl in the absence of offending medications), haemolytic anaemia
Renal involvement	Proteinuria (> 0.5 g/dl or 3+ positive on dipstick testing) or cellular casts
ANAs (antinuclear antibodies)	Higher titers generally more specific (> 1:160); must be in the absence of medications associated with drug-induced lupus
Immunologic phenomena	Anti-double-stranded DNA, anti-Smith (Sm) antibodies; antiphospholipid antibodies (anticardiolipin immunoglobulin G (IgG) or immunoglobulin M (IgM) or lupus anticoagulant); biologic false-positive serologic test results for syphilis, lupus erythematosus (LE) cells (omitted in 1997)
Neurologic disorder	Seizures or psychosis in the absence of other causes
Malar rash	Fixed erythema over the cheeks and nasal bridge, flat or raised
Discoid rash	Erythematous raised-rimmed lesions with keratotic scaling and follicular plugging, often scarring

Table III
The 1982 American College of Rheumatology (ACR) criteria summarise features necessary to diagnose systemic lupus erythematosus (SLE). They are summarised here with a useful mnemonic: the acronym "SOAP BRAIN MD". The presence of 4 of the 11 criteria yields a sensitivity of 85% and a specificity of 95% for SLE. It must be considered that individual features are variably sensitive and specific. Patients with SLE may present with any combination of clinical features and serologic evidence of lupus [7,8]

on the periferic blood was negative. The cytogenetic revealed a XY karyotype. In bone marrow cultures there was a lack of growth of BFU-E (Burst Forming Unit-Erythroid) and CFU-GM (Colony Forming Unit-Granulocyte, Macrofage).

Among the laboratory tests, the *Parvovirus* B19, the HIV, the CMV, and the EBV-Toxo Monotest were negative. There were no signs of haemolysis (LDH, haptoglobin, direct and indirect Coombs' tests were negative, schistocytes not on peripheral blood) and not obvious signs (clinical and laboratory) of viral disease. The Epo-Hb electrophoresis was in range, tumour markers were normal, and proteinaemia and serum electrophoresis were in range. After all examinations, we diagnosed pure red cell aplasia.

In August 2009 we started immunosuppressive therapy with cyclosporin and prednisone 25 mg + 200 mg + 250 mg/day with poor response (in fact the patient was transfused with two bags of erythrocytes every 15 days). From November 2009 to February 2010 testosterone undecanoate 50 mg was added to cyclosporin, with haemoglobin levels ranging from 7.2 and 8.9. In total, the patient was transfused with 40 bags of blood and ferritin 4,079 ng/dl.

The 2nd of February 2010 during the ambulatory monitoring appeared a swelling on the right laterocervical and on the tongue. Then the patient was sent to Maxillofacial Department where a biopsy was made and its specimen was later diagnosed of squamous cell carcinoma on the base of the tongue pN2b pT4. Subsequently he was submitted to subglottic laryngectomy + right lymphadenectomy + right laterocervical and then there was a plastic reconstruction and subsequently radiotherapy. After radiotherapy a hyperhaemia on the head and neck and dysfagia appeared.

During the following 6 months no trasfusion was necessary and the patient maintained the level of 9.5 g/dl of haemoglobin. Unfortunately, about 4 months after the patient had to receive transfusion every 20 days.

DISCUSSION

The description of this case is useful to point out the polymorphic features of paraneoplastic syndromes. In fact at the beginning there were suspected symptoms of systemic lupus erythematosus (SLE) but the examinations did not meet all the criteria of the American College of Rheumathology (Table III).

Because of the above-mentioned symptoms a steroid therapy was given. Subsequently the patient was again admitted to the hospital for severe megaloblastic anaemia: radiological, endoscopic, and serological investigations excluded causes of blood loss from the digestive tract, and eventual malabsorption and haemolysis.

The bone biopsy showed a series of red cell aplasia with a lymphoid infiltrate of reactive elements consistent with this histological result; the patient was transferred to the Department of Haematology, where the investigations were completed with the study of cell cultures of the erythroid series, that showed no basal growth and stimulation of growth factors, thus confirming the diagnosis of PRCA, but it was not yet clear if there was a primary or a secondary form

of subclinical autoimmune disease (erythroblastopenia in SLE).

In August 2009 the patient began a therapy with prednisone 25 mg and cyclosporin 600 mg/day; blood transfusions were required every 15 days, as the steroid therapy alone was not sufficient to maintain acceptable levels of haemoglobin.

In November 2009 the patient received 40 bags of transfused red cell concentrates and we decided therefore to associate also androgens (testosterone undecanoate) 50 mg and if after three months there was an improvement of haemoglobin, he could have started the serum anti-lymphocyte.

In October 2010, because of the appearance of laterocervical and lingual enlarged lymphnodes, the patient was transferred to the Department of Maxillofacial Surgery, where the biopsy was diagnosed with squamous cell carcinoma of the tongue pN2b pT4 (subglottic laryngectomy + right lymphadenectomy + right laterocervical with a plastic reconstruction); subsequently a radiotherapy was performed.

After surgery the patient wasn't transfused for about 6 months. The haemoglobin maintained the values of 9-9.8 g/dl and then the haemotransfusion was performed every 20 days.

A bone marrow biopsy control showed a slight increase of erythroid series: in this case we point out the absence in the literature of associations between pure red cell aplasia and squamous cell carcinoma of the tongue and that the removal of the tumour, as it happens in many paraneoplastic syndromes, shows the improvement of the clinical picture.

In this case the improvement of anaemia is connected to debulky cancer, to cytokines and to antibodies produced by the tumour.

The diagnosis of a paraneoplastic syndrome (PNS) may precede, follow or be concurrent with the diagnosis of a malignant tumour [9].

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DISCLOSURE

The Authors declare that they have no financial competing interests.

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