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CASE REPORT

Acute myelomonocytic leukaemia and pernicious anaemia in a patient with systemic lupus erythematosus: a rare coexistence of three immunological disorders

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Introduction

This article presents the case of a woman who presented simultaneously with systemic lupus erythematosus, acute myelomonocytic leukaemia and pernicious anaemia. As far as the authors know, this is the first report of this combination of pathologies that have an alteration in the immune system in common. Such association can be accidental, but the authors suggest that the aberrant expression of CD19+ B cells, that are frequently identified in acute myelomonocytic leukaemia and have been implicated in the pathogenesis of systemic lupus erythematosus, has a role in this association of autoimmune and neoplastic diseases.

Case report

A 19-year-old woman was treated at the Colima Regional University Hospital, Mexico, complaining of dyspnoea, cough, chest pain and marked weakness which had developed over the last 4 weeks. She had been taking oral ampicillin for 3 days 2 weeks before her admission without improvement, so had decided to go to the hospital. She reported a normal delivery 2 years earlier and no other relevant history. On admission to the emergency room, her blood pressure was 110/70 mmHg, heart rate 105 beats per minute and temperature 37.5°C; auscultation of the chest showed dullness and reduced vocal vibrations in the right lung base. Cardiac sounds showed a multifocal murmur. Examination of the skin revealed marked pallor and bruises on the arms. A chest radiograph showed a large pleural effusion at the right lung.

The initial laboratory results were haemoglobin 4.4 g/dl, with medium corpuscular volume of 112 fl, medium corpuscular haemoglobin 32.4 pg, total leucocytes 9300/dl, granulocytes 76%, lymphocytes 12%, monocytes 17%, platelets 38 000/dl and erythrocyte sedimentation rate 21 mm/hour. Blood chemistry, serum electrolytes and liver function tests were all normal. Drainage of the pleural effusion produced fluid with high protein content, and few mononuclear and red blood cells. A culture for *Mycobacteria tuberculosis* and the adenosine deaminase test were negative. A 24-hour urine sample showed proteinuria (560 mg/24 hours), with microscopic haematuria and granular casts. Cultures from blood, urine and pleural effusion were negative, as well as an HIV test. The first diagnosis was para-pneumonic pleural effusion, so she received intravenous ceftriaxone plus clarithromycin.

Haematological screening showed a reticulocyte count of 1.8%; a peripheral blood smear confirmed the presence of megaloblastic normochromic anaemia, low platelet count and marked monocytosis; ferritin and serum iron levels were normal, and her vitamin B_{12} level was low (120 pg/ml). Faecal occult blood test was negative. Pernicious anaemia was diagnosed, so the patient was started on intravenous cyanocobalamin, followed by oral hydroxocobalamin. Given the persistence of anaemia and thrombocytopenia, and as the pleural effusion was shown to be present on a new computed tomography scan, analysis of autoantibodies was requested that showed: positive antinuclear antibodies titre 1:320; anti-double stranded DNA with IFI+1:640; anti Smith negative. Complement C3 was 162 mg/dl, C4 was 15.6 mg/dl, anti-cardiolipin, antilupus coagulant and antithyroid antibodies were negative, and antibodies for antiparietal cells and anti-intrinsic factor were both positive. The rheumatologist diagnosed systemic lupus erythematosus and prescribed two intravenous boluses of methylprednisolone plus oral hydroxychloroquine. After this, the pleural effusion disappeared, her haemoglobin level increased to 7.2 g/dl, and she was discharged because of her clinical improvement.

Case report (continued)

However, she returned to the hospital with vaginal and gum bleeding, with peripheral purpuric lesions and thrombocytopenia (8000/dl), marked leukocytosis (42 000/dl) with monocytes 59%. A bone marrow biopsy yielded a remarkable hypercellularity, with 28% of normoblasts and 25% of large granulated myeloblasts without Auer bodies. A lymphocyte immunophenotyping showed a pattern of acute myeloid monoblastic leukaemia (AML type 4) with a positive aberrant expression of the lymphoid lineage: CD56+, CD19+. Chemotherapy was started with cytarabine A and doxorubicin, plus prednisone and hydroxocobalamin, which is her current treatment. After 4 months, the patient reported improvement in her weakness, with platelets 45 000/dl and haemoglobin 8.8 g/dl, without recurrence of pleural effusion.

Discussion

In the literature, there are 22 cases of the association between systemic lupus erythematosus and acute myeloid monoblastic leukaemia (Löfström et al, 2009; Massi et al, 2018). However, a relationship between these two conditions and pernicious anaemia does not seem to have been described before. The coexistence of three conditions apparently unrelated to each other in the same patient provoked intense debate among the authors and their colleagues. However, the clinical, immunological and pathological alterations are incontrovertible.

Regarding the possible pathophysiology of this comorbidity, most reports focus on the effect of immunosuppressive drugs (Ertz-Archambault et al, 2017). However other authors propose impaired phagocytosis of apoptotic cell material in patients with systemic lupus erythematosus, leading to abnormal apoptosis (Herrmann et al, 1998) and to an anarchic reproduction of oncogenic cells (Choi et al, 2017). On the other hand, aberrant expression of CD19+B with abnormal levels of $CD19^{hi}$ has been reported in patients with systemic lupus erythematosus (Liu et al, 2017) and, at the same time, a frequent aberrant expression of CD19+ in patients with acute myeloid monoblastic leukaemia type 4 (Francis et al, 2013). Such findings suggest a genetic alteration yet to be defined, which leads to aberrant expression of helper B lymphocytes, with an increase in cytopathic autoantibodies and, at the same time, a reduction in the ability to eliminate proto-oncogenic cells, particularly in lymphoid tissue (Herrmann et al, 1998).

For its part, the presence of pernicious anaemia seems to be an independent phenomenon, although some researchers have proposed that in patients with systemic lupus erythematosus, there are anti-parietal cell autoantibodies and anti-intrinsic factors (Song et al, 2019) that can produce pernicious anaemia and, with it, chronic vitamin B_{12} deficiency. This deficiency could also cause mutations in stem cell cytogenetics leading to myelodysplasia, and eventually to acute myeloid monoblastic leukaemia (Mufti et al, 1986; Drabick et al, 2001).

Learning points

- The present case, which appears to be the first report on this triple association (systemic lupus erythematosus, pernicious anaemia and acute myeloid monoblastic leukaemia), could not only increase knowledge of the complex interrelationship between clinical, genetic and immunogenic aspects, but also improve clinical suspicion of physicians when confronting atypical varieties of autoimmune diseases with signs of neoplasia in the medical consultation.
- The authors hypothesise that this patient had a primary aberrant dysregulation of CD19 lymphocytes, which contributed to the development of systemic lupus erythematosus, and secondarily to pernicious anaemia. Later, the combined deficiency of vitamin B_{12} and the aberrant CD19 evolved to acute myeloid monoblastic leukaemia.
- The favourable result so far with the use of chemotherapy, prednisone and vitamin B_{12} makes the authors suppose that such a combination could alter the primary dysregulation of B cells, a point that deserves further investigation.

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