# Síndrome de Evans — presentación atípica de un linfoma raro

## *Evans syndrome – atypical presentation of a rare lymphoma*

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## ABSTRACT

Evans Syndrome is a rare autoimmune condition characterized by two or more cytopenias, usually autoimmune haemolytic anaemia and immune thrombocytopenic purpura. It can be primary/idiopathic or secondary to other diseases. Authors describe an Evans syndrome case due to a splenic marginal zone lymphoma, a rare non-Hodgkin lymphoma.

**Keywords**: Evans syndrome; splenic marginal zone lymphoma, marginal zone lymphoma

## INTRODUCTION

Evans Syndrome (ES) is a rare autoimmune condition characterized by two or more cytopenias, occurring simultaneously or sequentially, autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenic purpura (ITP), and in 15% of cases also immune neutropenia[1]. ES is diagnosed in under 5% of all patients with AIHA or ITP and is more prevalent in female gender[2]. It can be primary/idiopathic or secondary, mostly to autoimmune, neoplastic, or infectious diseases.

## CASE REPORT

We present an 81-year-old female without any relevant medical background or regular medication, admitted due to a severe bicytopenia – anaemia (haemoglobin 5,7g/dl) and thrombocytopenia (72000/ul) – identified after complaints of asthenia, anorexia, and unquantified weight loss for 2 months. Clinically, she was emaciated, with discoloured skin and mucous membranes, slightly jaundiced, had a non-painful 2cm splenomegaly and no palpable lymphadenopathies. There was no history or evidence of haemorrhagic blood dyscrasia.

Blood tests (table 1) revealed haemolytic anaemia of autoimmune characteristics, namely, positive direct anti-globulin test, reticulocytosis, increased indirect bilirubin and LDH and decreased haptoglobin. These tests were performed before any transfusion support. Peripheral blood smear described anisocytosis and poikilocytosis, without platelet aggregates and without other morphological changes. Coagulation and liver tests were within reference values. Leukogram was normal and procalcitonin was negative. Infectious (table 1) and iatrogenic causes were excluded. Protein electrophoresis and serum immunofixation showed a small IgM monoclonal peak. A complementary autoimmune study (table 1) showed no alterations. Although controversial, search for antiplatelet antibodies was positive.

Because of the immune characteristics of the anaemia steroids were promptly initiated at admission (prednisolone 1mg/kg/day). Since the patient was so symptomatic it was decided, alongside the Immunohemotherapy department, to also provide a red blood cells transfusion which had poor analytical retort.

After two weeks of steroids there was no significant haemoglobin or platelets improvement. In the meanwhile, cranial-caudal CT scan showed a homogenous splenomegaly of about 18cm, with no evidence of neoformation or lymphadenopathies. Upper and lower digestive endoscopies with blind biopsies showed no changes and Helicobacter pylori was negative.

Peripheral blood immunophenotyping result was suggestive of a B-cell non-Hodgkin lymphoma, marginal zone type (MZL) (table 1). Bone biopsy using immunohistochemistry confirmed extensive medullary infiltration by MZL (figures 1 and 2). Splenic marginal zone lymphoma was assumed, and rituximab was started after Haematology specialist evaluation. Unfortunately, after only two weeks of treatment with rituximab she died in the set of respiratory sepsis.

Table 1. Blood tests

| BLOOD TESTS | | | | | |
|---|---|---|---|---|---|
| Haemoglobin (g/dl) | 5,4 | Prothrombin time (s) | 12,7 | Erythrocyte sedimentation rate (mm/h) | 121 |
| Haematocrit (%) | 17,8 | INR | 1,07 | Direct antiglobulin test | Positive |
| Average globular volume (fl) | 94,7 | Iron (ug/dl) | 35 | Antiplatelet antibody | Positive |
| Average globular haemoglobin (pg) | 28,7 | Transferrin (mg/dl) | 75 | IgG (mg/dl) | 563 |
| Reticulocyte (%) | 2,6 | Total iron binding capacity (ug/dl) | 105 | IgA (mg/dl) | 45 |
| Leukocyte (/ul) | 6500 | Ferritin (ng/ml) | 734 | IgM (mg/dl) | 217 |
| Neutrophils (/ul) | 4000 | B12 vitamin (pg/ml) | 150 | Kappa light chains (mg/dl) | 435 |
| Lymphocyte (/ul) | 1800 | Folate (ng/ml) | 3,4 | Lambda light chains (mg/dl) | <78,9 |
| Monocyte (/ul) | 600 | Haptoglobin (mg/dl) | <10 | Serum immunofixation | IgM band |
| Eosinophile (/ul) | 0 | Total bilirubin (mg/dl) | 5,9 | Protein electrophoresis<br>- albumin (g/dl)<br>- alfa1-globulin (g/dl)<br>- alfa2-globulin (g/dl)<br>- beta-globulin (g/dl)<br>- gama-globulin (g/dl) | <br>- 2,0<br>- 0,33<br>- 0,43<br>- 2,92<br>- 0,60 |
| Basophile (/ul) | 0 | Direct bilirubin (mg/dl) | 1,8 | | |
| Platelets (/ul) | 72000 | Lactate dehydrogenase (U/L) | 587 | | |
| Infectious panel | | | | | |
| HIV-1 and HIV-2 | | Negatives | | | |
| HBs Ag | | Negative | | | |
| Anti-HBc ab | | Negative | | | |
| Anti-HCV ab | | Negative | | | |
| CMV IgG | | Negative | | | |
| CMV IgM | | Negative | | | |
| EBV IgG | | Negative | | | |
| EBV IgM | | Negative | | | |
| Autoimmunity panel | | | | | |
| ANA | | Negative | | | |
| dsDNA | | Negative | | | |
| Lupic anticoagulante | | Negative | | | |
| IgG Anti-cardiolipin ab | | Negative | | | |
| IgM Anti-cardiolipin ab | | Negative | | | |
| IgG Anti-B2-glicoprotein-I ab | | Negative | | | |
| IgM Anti-B2-glicoprotein-I ab | | Negative | | | |
| Peripheral blood immunophenotyping | | | | | |
| Pathological B lymphocye population, monoclonal, kappa +, 0,4% of total cellularity (CD19+, CD20+ strong and homogeneous, CD5-, CD23-, CD79b+, CD31+ weak, CD305-, CD103-, CD10-/+, CD22+, CD11c-, CD45+, CD38-, CD200-/+, CD43- IgM-, CD27+, CD81+, CD25+) | | | | | |
| Conclusion: immunophenotype suggestive of B cell NHL, marginal zone type | | | | | |

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Figure 1. Bone marrow with intense hypercellularity due to extensive infiltration (about 70% of nucleated cells) by small to medium lymphoid cells, with an irregular nucleus and chromatin granularity (A: HE x40; B: HE x100).

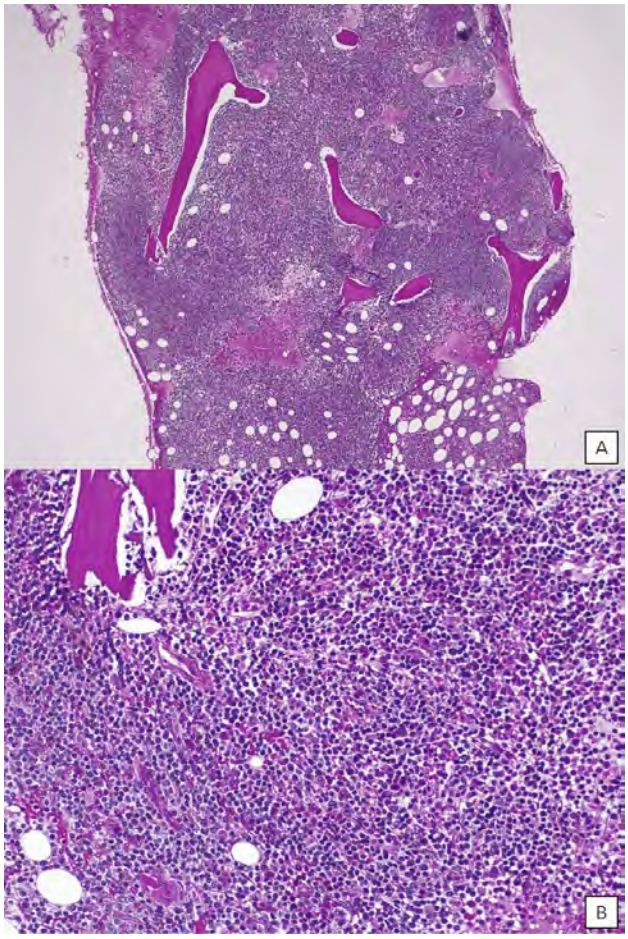
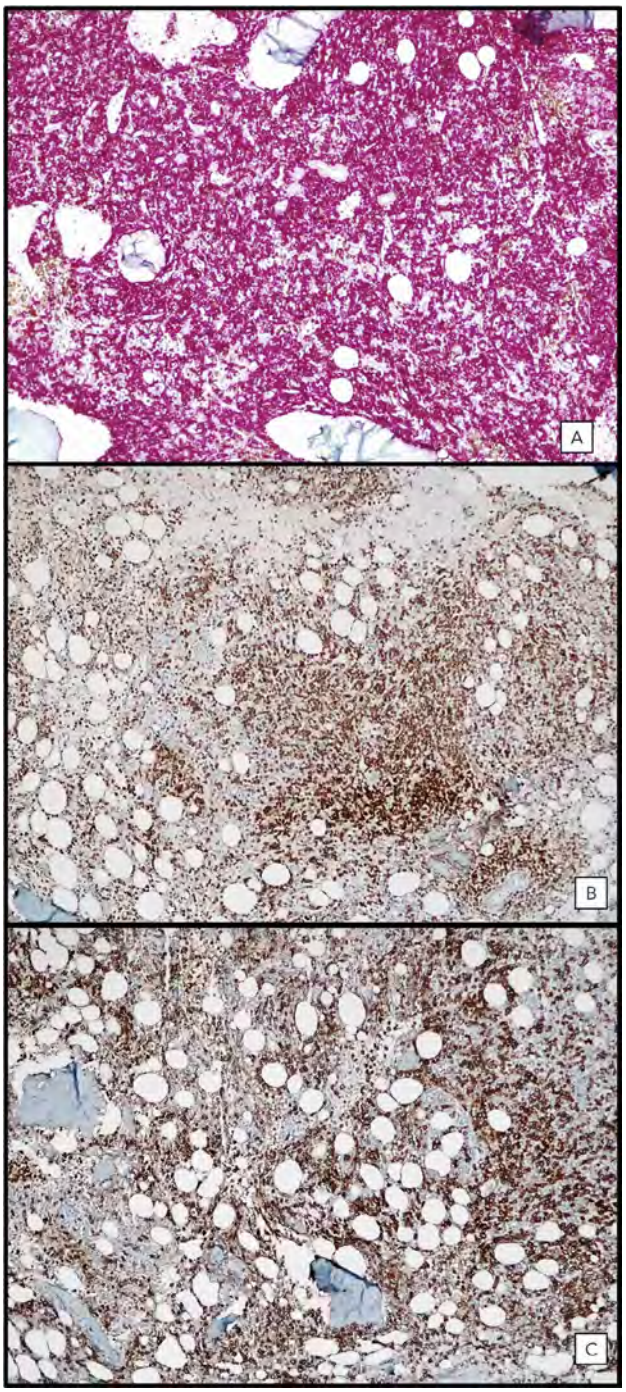



Figure 2. Immunohistochemical profile (A: CD20 + and CD3 +; B: bcl-2 +; C: CD43 +).




## DISCUSSION

MZL represents about 5-15% of all non-Hodgkin lymphomas (NHL)[3] and according to World Health Organization, they are categorized as mucosa-associated lymphoid tissue (MALT), splenic and ganglionic MZL. Splenic MZL is rare, accounting for 20% of all MZL and less than 1% of all NHL[3,4]. Average age at diagnosis is 69 years old and is slightly more frequent in males[5].

Splenic MZL diagnosis can be made without a splenic biopsy, as in our patient, using the combination of peripheral blood immunophenotyping and histology, and immunohistochemical analysis of bone biopsy.[3,5] Our patient had peripheral blood and bone marrow involvement, present in 95% of splenic MZL[6,7].

Usually, this lymphoma has an indolent behaviour, but in advanced stages, signs and symptoms related to splenomegaly can occur. Only 25% of patients have B symptoms and increased LDH at diagnosis, as seen in this case report[4,8].

Our patient presented with a severe new onset bicytopenia since she had normal blood tests from about 1,5 years ago. AIHA diagnosis was made based on the haemolytic characteristics and positive direct anti-globulin test. ITP diagnosis relied on the exclusion of alternative disorders. Drug-induced thrombocytopenia, infections, liver disease and microangiopatic processes were excluded as previously described. Positive antiplatelet antibodies were present, but they are not necessary in order to establish diagnosis. In 20% of cases, splenic MZL is associated with autoimmune manifestations such as AIHA and ITP however, combination of AIHA and ITP (ES) at presentation, as described in this case, is rare[3,8].

ES diagnosis implies the presence of AIHA and ITP and, rarely, association of immune neutropenia. True incidence in unidentified, but it is known to occur in less than 5% of all patients with AIHA and ITP and to be more prevalent in females [1,2,10]. Primary ES is an exclusion diagnosis and secondary ES has been associated with diseases such as systemic lupus erythematosus, anti-phospholipid antibody syndrome, Sjögren's syndrome, chronic lymphocytic leukaemia, NHL, hepatitis C, among others [1,9]. ES first-line treatment is prednisolone (1-2mg/kg/day) however, in secondary ES like in our case, treatment aimed at the underlying disease is paramount. Recommendations for splenic MZL treatment are symptomatic splenomegaly, cytopenias, systemic symptoms or disease progression [3,6]. Our patient had multiple treatment indications. Rituximab alone or with chemotherapy are the preferrable choices. In this case, rituximab was particularly indicated due to ES, allowing to control the underlying disease and have a faster resolution of immune cytopenias[3,6].

About one third of patients with splenic MZL present with monoclonal

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gammopathy, usually IgM and at low levels (<2g/dl), as described in our patient; presence of this paraprotein seems to be related to advanced disease and bone marrow invasion, and is associated with a worse prognosis[3,9,11].

## CONCLUSION

ES is rare but is believed to be underdiagnosed and, as such, in presence of a new onset anaemia and thrombocytopenia, simultaneous or sequential, this diagnostic hypothesis must be considered. Primary ES is an exclusion diagnosis, and it is much more frequent to occur associated with another disease, usually autoimmune, infectious, or lymphoproliferative, and that is why it is necessary to carry out a detailed complementary study.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this work.

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This research had no funding sources.

### ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

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