International Journal of Gerontology xxx (2014) 1–3

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Case Report

Evans Syndrome Presented with Marginal Zone Lymphoma and Duodenal Neuroendocrine Tumor in an Elderly Woman☆

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ARTICLE INFO

Article history:
Received 28 November 2012
Received in revised form
20 May 2013
Accepted 16 August 2013
Available online xxx

Keywords:
Evans syndrome,
influenza vaccine,
lymphoma,
neuroendocrine tumor,
triggers

SUMMARY

Evans syndrome (ES) is an autoimmune disorder characterized by simultaneous or sequential development of autoimmune hemolytic anemia, immune thrombocytopenia, and/or neutropenia. ES can be classified as a primary (idiopathic) or secondary (associated with an underlying disease) syndrome. We report a case of ES in an elderly patient in the presence of multiple trigger factors such as recent influenza vaccine, marginal zone lymphoma, and neuroendocrine tumor G1. Whether this association is casual or causal remains a matter of speculation. It is however necessary to have a thorough work-up in a newly diagnosed ES and a more accurate search of miscellaneous factors especially in elderly patients.

1. Introduction

Evans syndrome (ES) includes acquired autoimmune, hemolytic anemia, and thrombocytopenia and has been described very recently[1,2]. It is more frequent in adult women and has usually been reported during pregnancy. We report a case of ES in an elderly patient in the presence of multiple trigger factors such as recent influenza vaccine, marginal zone lymphoma, and neuroendocrine tumor G1.

2. Case report

A 73-year-old female presented to the emergency department (ED) complaining of malaise, asthenia, dyspnea on mild effort, and emission of hypercromic urine occurring 7 days after administration of the influenza vaccine. The medical history of the patient included diabetes mellitus, chronic obstructive pulmonary disease, hypertension, and hypothyroidism, and her usual medications consisted of an oral hypoglycemic agent (sitagliptin), antihypertensive medications (losartan plus hydrochlorothiazide), L-thyroxine, and long-acting β agonist (indacaterol). Steroid treatment (prednisone 25 mg *per os*) was initially started at home without any improvement. At admission, her vital signs were normal and the patient was not in acute distress; her heart, lungs, and abdominal examinations were unremarkable, except for mild splenomegaly, and she had no evidence of lymphoadenopathy or signs of bleeding diathesis. The preliminary laboratory tests revealed a white blood cell (WBC) count of 6.7 x 10^9/L, hemoglobin (Hb) of 8.4 g/L, hematocrit of 25.5%, and platelet count (PLT) of 252 x 10^9/L, elevated values of lactate dehydrogenase (980 U/L), consumed haptoglobin, and direct antiglobulin test anti-IgG positive. Furthermore, laboratory tests showed normal values of liver function, prothrombin time (PT), partial thromboplastin time (PTT), serum protein electrophoresis, serum immunoglobulin concentration, and negativity of antinuclear antibodies, HIV, hepatitis A, B, and C serology tests.

After hematological consultation, we started therapy with oral prednisone 1 mg/kg plus intravenous immunoglobulin (IVIG) of

☆ None of the authors has any financial interest related to the manuscript.

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http://dx.doi.org/10.1016/j.ijge.2013.08.006

0.6 g/kg daily, with a gradual increase of hemoglobin count to 9.4 g/dL at the 8th day (Table 1). Beginning on the 10th day, we observed a rapid decrease in platelet counts at the 20th day (21 k/μL). The laboratory findings revealed the presence of platelet antigen-specific antibodies, and a normal peripheral blood smear excluded pseudothrombocytopenia. At the 20th day, administration of prednisone was stopped and dexamethasone plus IVIG 0.6 g/kg for 5 days was intravenously administered. At the 25th day, oral prednisone was administered. Bone marrow aspirate and core biopsy (Fig. 1A and B) showed hypercellular marrow with nodular and paratrabecular infiltration of small B lymphocytes. Immunophenotypic analysis of peripheral blood showed a monoclonal B lymphocyte $CD20^{+}CD5^{-}CD10^{-}$ population (Fig. 1C), compatible with marginal zone lymphoma. The ultrasound examination showed mild splenomegaly with no other abnormalities. The abdominal computed tomographic (CT) scan revealed a neoformation on the endoluminal side of the duodenum near the papilla of Vater. Esophagogastroduodenoscopy and biopsy confirmed the presence of a polypoid lesion at the second portion of the duodenum, with histological findings indicating a neuroendocrine tumor (NET) G1. Chromogranin A was 363 ng/mL (normal between 20 ng/mL and 100 ng/mL), whereas all other hormones were within normal limits, including urinary 5-hydroxyindoloacetic acid. Anterior planar view of the abdomen 24 hours and 48 hours after injection of 120 MBq 111I Pentetreotide (octreoscan) was strongly suggestive of high amounts of somatostatin receptors in the duodenum. The oncologist decided to follow-up NET without starting therapy while the hematologist suggested close monitoring for indolent lymphoma. Laboratory tests at the time of discharge revealed: WBC 10.5 k/μL, Hb 12.9 g/dL, Hct 40.4%, and PLT 334 k/μL.

3. Discussion

ES is an autoimmune disorder defined by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP), and/or immune neutropenia[1,2]. Since first described in the early 1950s, ES has long been considered as a rather incidental and "anecdotal" combination of ITP and AIHA and/or autoimmune neutropenia in the absence of any underlying cause. The largest survey of ES published to date reviewed 68 patients with a mean age of 52 ± 33 years[3]. In this study, ES was considered idiopathic in 34 patients but an underlying disorder, such as systemic lupus erythematosus, lymphoproliferative disorders, or primary immunodeficiences, was detected in half of these cases[3]. We also found a report of ES following influenza vaccine[4], as well as its association with miscellaneous diseases such as enterochromaffin-like tumor[5]. ES is more than a coincidental combination of immune cytopenias, but rather a chronic state of profound dysregulation of the immune system that may be associated with other autoimmune or lymphoproliferative disorders as well as primary immunodeficiencies[6]. Corticosteroids remain the cornerstone of treatment, with an initially large response (80%), but eventually up to two-thirds of patients are provided with at least one second-line treatment, mostly to spare corticosteroids. IVIG represents another first-step therapy, especially in the presence of ITP. As a second-line treatment, rituximab is now worth considering before splenectomy and/or the use of immunosuppressors in patients who have a chronic and corticosteroid-dependent ES; splenectomy, danazol-specific immunosuppressants (intravenous

Table 1
Correlation between clinical–laboratoristic course and treatment.

Day of hospitalization	Hb level (g/dL)	Platelet count (k/μL)	Therapy
1st	8.4	308	Prednisone 75 mg + IVIG 0.6 g/kg
8th	9.4	267	Prednisone 50 mg
10th	9.9	128	Prednisone 50 mg
15th	10.8	54	Prednisone 50 mg
20th	9.2	21	Dexamethasone 40 mg + IVIG 0.6 g/kg
25th	9.9	27	Prednisone 75 mg
30th	10.8	28	Prednisone 75 mg
35th	11.5	28	Prednisone 75 mg
40th	11.2	64	Prednisone 50 mg
45th	12.4	140	Prednisone 37.5 mg
50th	12.5	241	Prednisone 37.5 mg
60th	12.9	334	Prednisone 25 mg

IVIG = intravenous immunoglobulin.

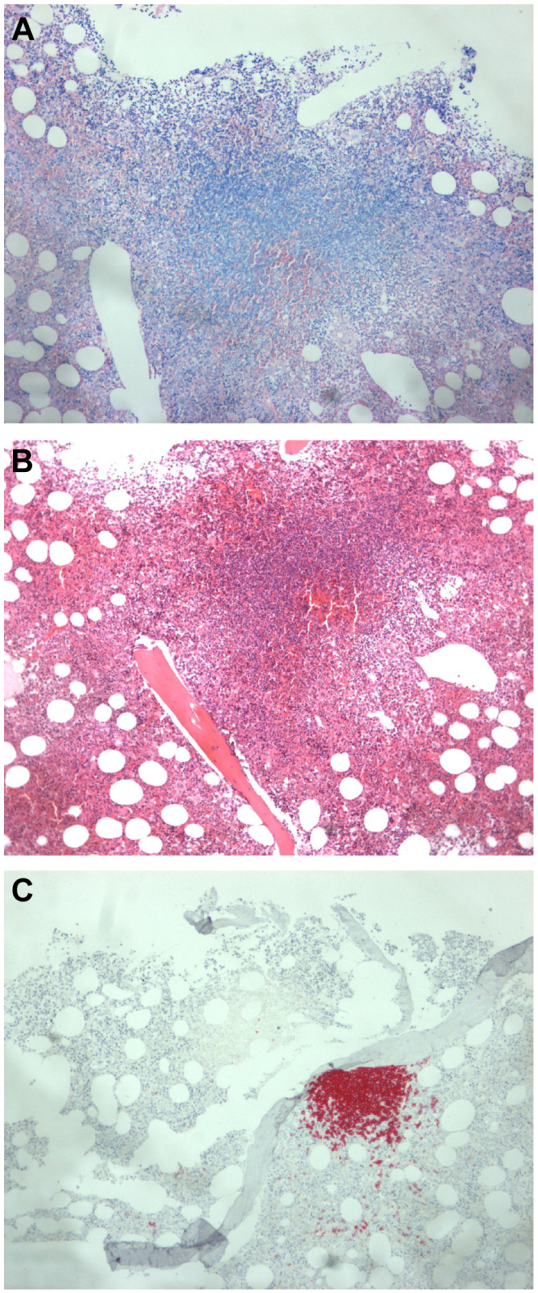

Fig. 1. Morphological analysis of sections of bone marrow revealed nodular and paratrabecular infiltration of small B lymphocyte (A, B), whereas immunophenotypic analysis (C) with fast red chromogen for CD20 antigen showed a monoclonal B lymphocyte $CD20^{+}CD5^{-}CD10^{-}$ population (C), compatible with marginal zone lymphoma.

Please cite this article in press as: D'Ambrosio D, et al., Evans Syndrome Presented with Marginal Zone Lymphoma and Duodenal Neuroendocrine Tumor in an Elderly Woman, International Journal of Gerontology (2014), http://dx.doi.org/10.1016/j.ijge.2013.08.006

cyclophosphamide, cyclosporin, or azathioprine) and more recently mycophenolate mofetil represent alternative strategies[7].

In our case report, we found multiple factors that could trigger ES, such as influenza vaccine, indolent lymphoma, and NET.

To the best of our knowledge, this is the first case of ES associated with concomitant multiple trigger factors. Whether this association is casual remains a matter of speculation. Immunizations and lymphoproliferative disorders may provide a trigger for the development of autoimmune disease in susceptible individuals, such as in an elderly patient[8]. Marginal zone B cells have been shown to initiate immune responses by transporting IgM antigen immune complexes into the follicle[9]. This mechanism may play an important role in the removal of senescent cells, apoptotic debris, and immune complexes[9]. A migration of neoplastic cells with immune complexes and autoantigens to the bone marrow occurs in patients with marginal zone lymphoma. Abnormally expanded γδ T cells could also provide increased amounts of T helper cells to B cells to produce autoantibodies[9]. Type 1 gastrointestinal carcinoid tumors are associated with type 1 chronic atrophic gastritis, achlorhydria, and pernicious anemia, while only one case has been reported in ES[5]. An association between carcinoid and other non-carcinoid malignancies has been reported in up to 22% of cases[10]. Moreover, the coexistence of NET and mucosa-associated lymphoid tissue lymphoma in the gastrointestinal tract was also reported in the literature suggesting a common etiology (i.e., *Helicobacter pylori* infection)[11–13]. In our case, the presence of multiple possible triggers for ES could be synergistic and explain, at least in part, the slow rise of platelet counts and the resistance to medical treatment. Accordingly, all triggers are very critical points in advancing age[14,15].

In conclusion, the possibility of age-related multiple comorbidities with ES should not be neglected. It is therefore necessary for a thorough work-up in a newly diagnosed ES patient, and a more accurate search of miscellaneous factors, especially in elderly patients to whom comorbidity may be a mask of the underlying disease.

Acknowledgments

We would like to thank Elda Feyles, MD, and Daniele Ricci, MD (from the Division of Pathologic Anatomy, Cardinal Massaia Hospital, Asti, Italy) for their helpful assistance. We would also like to thank Carl S. Wilkins (FIU Herbert Wertheim College of Medicine, Miami, FL, USA) and Hung Wen (Department of Neurology Cerebral Vascular Disease Research Center, University of Miami Miller School of Medicine, FL, USA) for their helpful assistance in English language.

References

1. Evans RS, Takahashi K, Duane RT, Payne R, Liu C. Primary thrombocytopenic purpura and acquired haemolytic anemia; evidence for a common etiology. *Arch Int Med*. 1951;93:341–344.
2. Evans RS, Duane RT. Acquired hemolytic anemia; the relation of erythrocyte antibody production to activity of the disease; the significance of thrombocytopenia and leukopenia. *Blood*. 1949;4:1196–1213.
3. Michel M, Chanet V, Dechartres A, et al. The spectrum of Evans' syndrome in adults: new insight into the disease based on the analysis of 68 cases. *Blood*. 2009;114:3167–3172.
4. Shlamovitz GZ, Johar S. A case of Evans' syndrome following influenza vaccine. *J Emerg Med*. 2013;44:e149–e151.
5. Baltayiannis GE, Katsanos KH, Fotopoulos A, Tsianos EV. Evans' syndrome and enterochromaffin-like tumour (ECLoma). *Ann Gastroenterol*. 2003;16:74–75.
6. Wang W, Herrod H, Pui CH, Presbury G, Wilimas J. Immunoregulatory abnormalities in Evans' syndrome. *Am J Hematol*. 1983;15:381–390.
7. Norton A, Roberts I. Management of Evans' syndrome. *Br J Haematol*. 2005;132:125–137.
8. Hauswirth AW, Skrabs C, Schützinger C, Gaiger A, Lechner K, Jäger U. Autoimmune hemolytic anemias, Evans' syndromes, and pure red cell aplasia in non-Hodgkin lymphomas. *Leuk Lymphoma*. 2007;48:1139–1149.
9. García-Munoz R, Rodriguez-Otero P, Pegenaute C, et al. Splenic marginal zone lymphoma with Evans' syndrome, autoimmunity, and peripheral gamma/delta T cells. *Ann Hematol*. 2009;88:177–178.
10. Hiripi E, Bermejo JL, Sundquist J, Hemminki K. Familial gastrointestinal carcinoid tumours and associated cancers. *Ann Oncol*. 2009;20:950–954.
11. McGregor DH, Cherian R, Weston AP, Lawson L, McAnaw MP. Adenocarcinoid of ileum and appendix, incidentally discovered during exploratory laparotomy for gastric MALT lymphoma, with subsequent diffuse prostatic metastases: report of a case with light, immunohistochemical, and electron microscopic studies. *Dig Dis Sci*. 1999;44:87–95.
12. Burkitt MD, Pritchard DM. Pathogenesis and management of gastric carcinoid tumours. *Aliment Pharmacol Ther*. 2006;24:1305–1320.
13. Parsonnet J, Hansen S, Rodríguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med*. 1994;330:1267–1271.
14. Thewissen M, Stinissen P. New concepts on the pathogenesis of autoimmune diseases: a role for immune homeostasis, immunoregulation, and immunosenescence. *Crit Rev Immunol*. 2008;28:363–376.
15. Mazzella F, Cacciatore F, Galizia G, et al. Social support and long-term mortality in the elderly: role of comorbidity. *Arch Gerontol Geriatr*. 2010;51:323–328.

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