Clinical Oncology: Case Reports

Case Report

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Paraneoplastic Evans Syndrome Associated with Serous Ovarian Carcinoma

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Abstract

Evans Syndrome (ES) is a rare condition defined by the co-occurrence of two or more immune cytopenias, most frequently Autoimmune Hemolytic Anemia (AIHA) and Immune Thrombocytopenia (ITP). This condition is associated with a wide range of disease processes including infectious, autoimmune, or malignant etiologies. Paraneoplastic Evans syndrome is most often associated with hematological malignancies such as Chronic Lymphocytic Leukemia (CLL) or Non-Hodgkin Lymphoma (NHL), and while exceedingly rare, ES has also been reported in solid tumors. ES is considered more difficult to treat than isolated ITP or AIHA, with higher rates of treatment failure and disease recurrence. Corticosteroids are the cornerstone of therapy, but other treatment options including intravenous immunoglobulins, immunosuppressants, and hematopoietic stem cell transplantation have also been used. In this article, we report a case of a seventy-one-year-old female who had undiagnosed serous ovarian carcinoma with paraneoplastic Evans syndrome as the initial presentation. She developed signs of elevated intracranial pressure including headache, nausea and vomiting at home and was found to have life-threatening intracranial hemorrhage from ITP, in addition to critical anemia from AIHA. She responded well to treatment and survived the episode, after which her ES was controlled with chronic low-dose steroids. Extensive diagnostic workups for secondary causes of ES were unrevealing at the time, although a solid right adnexal mass was incidentally found. The lesion was not urgently investigated and periodic surveillance was preferred over prompt surgical resection. A few months later she was found to have extensive metastases from high-grade serous ovarian carcinoma and died shortly after chemotherapy was initiated. Her missed diagnosis can be attributed to a general lack of awareness of the association between ES and solid tumors. She succumbed to the cancer which, if detected early, was arguably curable. In light of this tragedy, it is our intention to raise awareness of this rare disorder and its association with uncommon etiologies.

Keywords

Evans Syndrome; Autoimmune hemolytic anemia; Serous ovarian carcinoma; Paraneoplastic syndrome; Ovarian cancer

Introduction

Evans Syndrome (ES) is a rare condition characterized by the co-occurrence of two or more immune cytopenias, most often Autoimmune Hemolytic Anemia (AIHA) and Immune Thrombocytopenia (ITP). AIHA and ITP are autoimmune diseases whereby autoantibodies bind to self red blood cells and platelets, respectively, causing them to be destroyed. Both AIHA and ITP have been separately reported as paraneoplastic syndromes associated mainly with hematological malignancies such as Chronic Lymphocytic Leukemia (CLL) or non-Hodgkin Lymphoma (NHL). Rarely have these conditions been linked to solid tumors, however. Here, we present a very rare case of paraneoplastic Evans syndrome associated with ovarian cancer.

Case Presentation

A 71-year-old woman presented with headache, nausea, and vomiting for 7 days. She also developed new-onset petechiae in her legs for 3 weeks. Her past medical history includes hypertension, hyperlipidemia, seizure disorder, coronary artery disease, anxiety disorder, history of traumatic subdural hematoma status post craniotomy, and morbid obesity. Initial CBC showed critically low platelet count of 6000/uL and low hemoglobin of 8.4 g/dL. Head CT revealed moderate-sized parenchymal hematoma in right parietal lobe, moderate-sized subdural hematoma in left parietal lobe, and small amount of subarachnoid hemorrhage near the right vertex (Figure 1).

She was emergently transfused several units of platelet products and admitted to the Intensive Care Unit (ICU) for close neurological monitoring and blood pressure control with nicardipine infusions. A diagnosis of acute immune thrombocytopenia was made and empiric treatment with Intravenous Immune Globulins (IVIG) and high-dose steroids were initiated. Within 24 hours following admission her hemoglobin also dropped to a critically low level and emergency transfusions with packed red blood cells had to be given. A positive direct antiglobulin test (DAT) for IgG and complements confirmed the diagnosis of Warm Autoimmune Hemolytic Anemia (WAIHA). Her brain bleed eventually stopped while her red blood cell and platelet counts gradually normalized after several days of treatment.

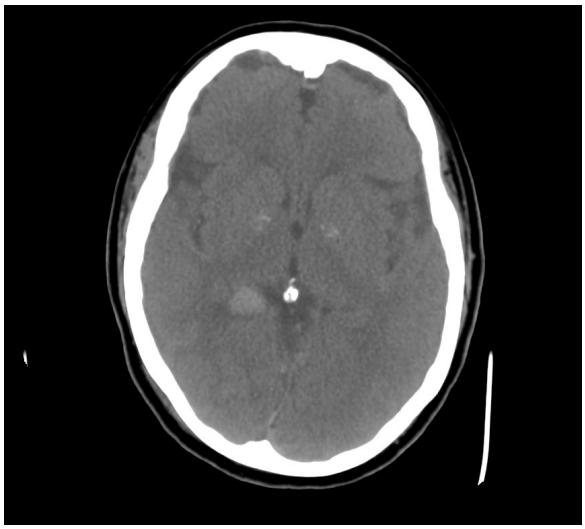

Figure 1: Moderate-sized parenchymal hematoma in right parietal lobe at time of initial presentation.

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Extensive diagnostic workups for the cause of her ITP and WAIHA including peripheral blood smear, bone marrow biopsy, and flow cytometry failed to show any evidence of hematological malignancies. Workups for possible infectious or rheumatological causes were also negative, and her tumor markers were within normal limit. Eventually she was discharged on oral steroids after being hospitalized for 2 weeks. During her hospital stay a solid right adnexal mass measuring 3.5 cm × 2.4 cm × 2.4 cm in size was incidentally found.

At an outpatient visit with gynecology a month later, her right adnexal mass had increased to 5.2 cm × 2.5 cm × 2.5 cm in size on transvaginal ultrasound. She did not opt for surgical removal at that time and it was decided that repeat ultrasound will be performed in 6 months for continued surveillance.

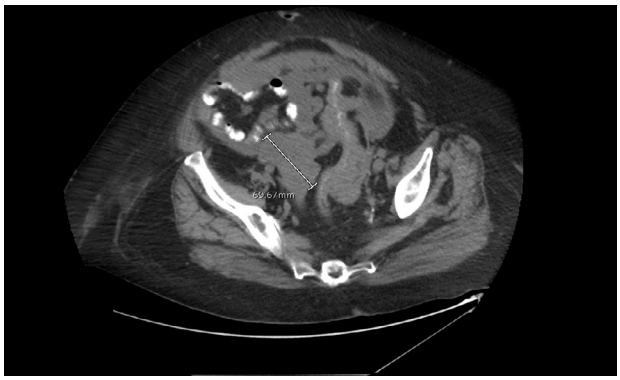

Figure 2: Right adnexal mass at time of her ovarian serous carcinoma diagnosis.

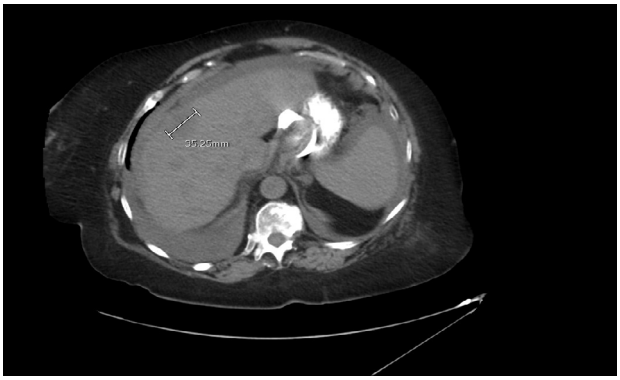

Figure 3: Diffuse hepatic metastases, including a large 3.5 cm liver mass, were found on CT abdomen.

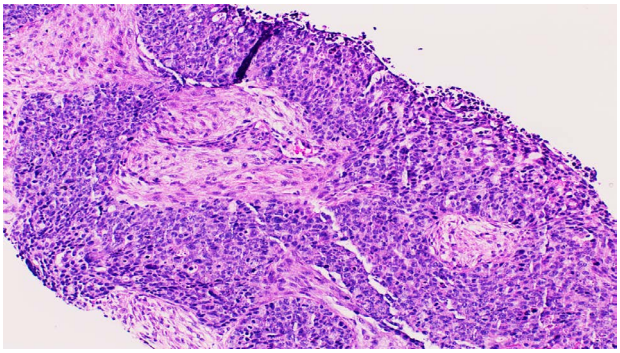

Figure 4: High-grade serous carcinoma cells (H+E x20).

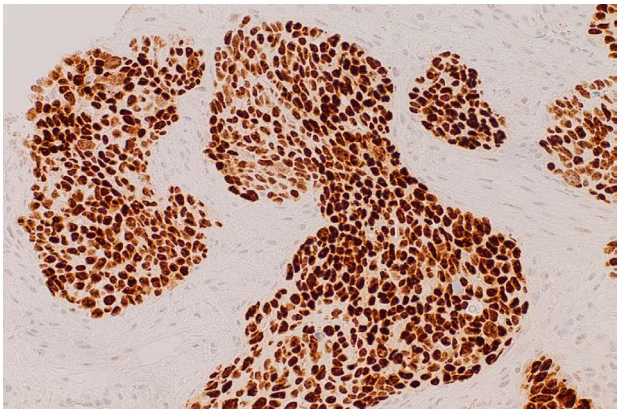

Figure 5: High-grade serous carcinoma cells with intense nuclear staining for PAX8 (x20).

About 6 months after her initial hospitalization for intracranial hemorrhage, she was again admitted to the hospital after developing progressively worsening abdominal pain following a fall at home. This time, Computed Tomography (CT) of abdomen and pelvis showed extensive masses involving the liver, peritoneum, and both ovaries. Her right adnexal mass had also grown to about 7 cm in size. She subsequently underwent biopsy of a peritoneal mass which turned out to be high-grade serous carcinoma of likely ovarian origin. She was also found to have significantly elevated CA-125 level of 1524 (Figure 2).

She was quickly started on neoadjuvant chemotherapy with carboplatin and paclitaxel. Unfortunately, she died from cancer-related complications shortly after her first cycle of chemotherapy (Figures 3-5).

Discussion

Evans syndrome is a very rare disease characterized by the development of two or more immune cytopenias, most commonly autoimmune hemolytic anemia and immune thrombocytopenia, with or without immune neutropenia. AIHA and ITP are immune-mediated processes whereby autoantibodies bind to and destroy self red blood cells and platelets, respectively.

Evans syndrome was first described in 1951 and is diagnosed in less than 5% of all patient with either ITP or AIHA, with mean age at the time of diagnosis at 52 years [1-3]. As is the case in most autoimmune conditions, ES has a female predilection with female to male ratio of 3:2 [2].

Evans syndrome can be either idiopathic (primary) or acquired (secondary) *via* association with an underlying condition such as viral infections (HIV, HCV, COVID-19), autoimmune diseases (SLE, CVID, ALPS), drug use (diclofenac, ramipril), certain types of cancer (NHL, CLL), or following bone marrow transplantation [2,4-7].

Warm AIHA constitutes approximately 70%-80% of all AIHAs, with the remainder comprising mainly of Cold-Agglutinin Disease (CAD) and other less common disorders. The type of AIHA that

presents in Evans syndrome is warm AIHA, in which IgG antibodies react with red blood cell surface antigens at body temperature [3] .

Both AIHA and ITP have frequently been reported as paraneoplastic syndromes of hematological malignancies such as Chronic Lymphocytic Leukemia (CLL) or non-Hodgkin Lymphoma (NHL) [8]. However, neither conditions are usually associated with solid tumors and only a handful of cases have been reported in which either paraneoplastic AIHA or ITP occurred as a result of an underlying non-hematological malignancy [9-11]. Paraneoplastic Evans syndrome, on the other hand, is exceedingly rare in solid tumors and was reported only once in the literature [5].

The presence of AIHA as a paraneoplastic syndrome of ovarian cancer is associated with poor overall prognosis [12]. One literature review in 2015 examined ten reported cases of paraneoplastic AIHA associated with ovarian tumors since 1945 and found that most had metastatic disease either on presentation or later during course of the disease [4]. Of those cases, papillary cystadenocarcinoma is the single most common type of ovarian malignancy involved, comprising 60% of all reported cases, followed by anaplastic carcinoma (20%) and other less common ovarian cancers [12].

Evans syndrome is considered more difficult to treat than isolated ITP or AIHA, with higher rates of treatment failure and disease recurrence [13]. Corticosteroids are the mainstay therapy, achieving an 83% initial response rate in one study [14]. Intravenous immunoglobulin, which acts by blocking the FCγ receptor on the macrophages, is frequently used in combination with steroids as the first-line therapy for ES. However, its use remains controversial due to high treatment cost, lack of supporting data, and reports of severe adverse effects [14]. Nevertheless, in cases of severe manifestations of ITP such as intracranial bleeding, timely use of IVIG can often be life-saving, as was the case in our patient.

Immunosuppressants, including rituximab, mofetil mycophenolate, cyclosporine, vincristine, azathioprine, sirolimus, and thrombopoetin receptor agonists, have been used as second-line treatment for refractory ES [14]. In resistant cases, Hematopoietic Stem Cell Transplantation (HSCT) has been used successfully and is currently the only curative treatment option for ES [15].

For paraneoplastic Evans syndrome, treatment of the underlying malignancy appears to be very effective at controlling the disease. In one case report from China, a patient with newly-diagnosed secondary ES associated with pulmonary papillary carcinoma achieved complete, long-lasting remission with prompt restoration of peripheral blood cell counts following lung cancer resection. Other studies have also shown sustained remission of paraneopastic AIHA, which were often refractory to treatment with steroids, after curative resection of the cancers [9,16,17].

In our case, the patient was diagnosed with high-grade serous ovarian carcinoma months after she was found to have Evans syndrome. To our best knowledge, this is the first reported case of secondary Evans syndrome associated with serous ovarian carcinoma.

Her ES was in remission after the initial episode and remained well-controlled on chronic steroids. Unfortunately, due to the extreme rarity of autoimmune cytopenia as a paraneoplastic syndrome of solid organ tumors and general lack of awareness of this association, this early warning sign was not recognized. As a result, her right adnexal mass was not surgically resected in due course, allowing her cancer to rapidly progress and eventually resulting in fatal outcome.

Conclusion

This case is unique in that autoimmune disorders such as AIHA and ITP, while commonly seen in lymphomas and leukemias, are rarely observed as paraneoplastic syndromes in solid tumors. Our patient simultaneously developed both autoimmune disorders, making her only the second person in known literature to have developed paraneoplastic Evans syndrome from a non-hematological malignancy. The delay in her ovarian cancer diagnosis can be attributed to a general lack of awareness among physicians of the association between paraneoplastic autoimmune disorders and solid tumors. In reporting her case, we hope to promote awareness and diagnosis of this rare condition, especially when it's associated with potentially fatal malignancies.

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