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SECONDARY EVANS SYNDROME ASSOCIATED WITH LOCALIZED CLEAR CELL RENAL CELL CARCINOMA: A CASE REPORT AND BRIEF LITERATURE REVIEW

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ABSTRACT

Introduction: Immune thrombocytopenia (ITP) and autoimmune haemolytic anaemia (AIHA) are uncommon paraneoplastic manifestations of solid tumours, and their association with renal cell carcinoma is exceptional.

Case description: A 66-year-old man with no prior medical history presented with profound thrombocytopenia (5 ×10^3/µl) and AIHA, confirmed by a strongly positive direct antiglobulin test with IgG and complement. Diagnostic work-up identified a left renal mass corresponding to localized clear cell renal cell carcinoma (pT1b). Bone marrow examination showed preserved megakaryopoiesis without dysplasia or infiltration, and peripheral smear confirmed true thrombocytopenia with macroplatelets. Thrombocytopenia persisted despite corticosteroids, intravenous immunoglobulin, and radical nephrectomy. Sustained platelet recovery was achieved with eltrombopag, a thrombopoietin receptor agonist (TPO-RA).

Conclusion: Secondary Evans syndrome associated with localized renal cell carcinoma is an exceptionally rare disorder. Persistence of cytopenias after surgical tumour control does not rule out a paraneoplastic mechanism, and TPO-RAs may represent an effective option in refractory cases, although evidence in secondary ITP remains limited.

KEYWORDS

Paraneoplastic syndrome, secondary Evans syndrome, immune thrombocytopenia, renal cell carcinoma, thrombopoietin receptor agonists

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LEARNING POINTS

- Secondary Evans syndrome (most commonly concurrent immune thrombocytopenia and autoimmune haemolytic anaemia) is an exceptionally rare paraneoplastic manifestation of localized clear cell renal cell carcinoma and requires rigorous diagnostic exclusion.
- Persistence of immune cytopenias for several weeks after curative nephrectomy does not exclude a paraneoplastic mechanism, as autoimmune activity may continue beyond tumour control.
- Thrombopoietin receptor agonists may be effective in immune thrombocytopenia secondary to solid tumours, a scenario with substantially less evidence than primary immune thrombocytopenia.

INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired disorder characterized by peripheral platelet destruction and inadequate platelet production, defined by a platelet count below 100 $\times 10^9$/l[1,2]. Approximately one-fifth of cases are associated with infections, autoimmune diseases, drugs, or malignancies (secondary ITP)[2,3]. Paraneoplastic ITP related to solid tumours is rare; it has been described predominantly in breast, lung, and gastrointestinal cancers, while its association with clear cell renal cell carcinoma is exceptional and is limited to isolated reports[4].

Evans syndrome is defined by the simultaneous or sequential occurrence of immune-mediated ITP and autoimmune haemolytic anaemia (AIHA) in the absence of an identifiable underlying cause; when it occurs in the context of an underlying condition (autoimmune, lymphoproliferative, infectious, or neoplastic), it is termed secondary Evans syndrome[5]. We report a case consistent with secondary Evans syndrome associated with localized clear cell renal cell carcinoma, with emphasis on the differential diagnosis, the postoperative temporal course, and the therapeutic response to a thrombopoietin receptor agonist (TPO-RA).

CASE DESCRIPTION

A 66-year-old man with no prior medical history was referred from the occupational medicine service after incidental detection of anaemia and severe thrombocytopenia on routine laboratory testing. On admission, he presented with pallor, ecchymoses, and petechiae, without major bleeding. Initial complete blood count showed haemoglobin 8.5 g/dl (reference range 14–16.5 g/dl), platelets 5 $\times 10^3$/µl (reference range130–400 $\times 10^3$/µl), and leukocytes 13.63 $\times 10^3$/µl (reference range 4–11 $\times 10^3$/µl) with neutrophilia. Clinical and imaging evaluation revealed no hepatomegaly or splenomegaly.

Autoimmune haemolytic anaemia was confirmed by a direct antiglobulin test of 4+, with IgG 3+, IgA 1+, IgM 1+, C3c 1+, and C3d 3+; total bilirubin 2.83 mg/dl (reference range 0.3–1.2 mg/dl), indirect bilirubin 2.28 mg/dl, haptoglobin 15 mg/dl (reference range 30–200 mg/dl), and lactate dehydrogenase 612 U/l (reference range 135–225 U/l). The serological pattern, with predominant IgG and complement activation (C3d 3+) accompanied by minor positivity for IgA and IgM, is consistent with warm AIHA with a complement-mediated component; the unusual co-expression of three immunoglobulin classes may reflect a broadened immune response, a finding of interest in the paraneoplastic context.

The coagulation profile did not support overt disseminated intravascular coagulation: the international normalised ratio and activated partial thromboplastin time were normal, fibrinogen remained between 189 and 229 mg/dl (200–400), and D-dimer was within the normal range. Etiologic work-up was negative for human immunodeficiency virus, hepatitis C virus, and *Helicobacter pylori*; antinuclear antibodies and the extractable nuclear antigen panel were non-reactive. Hepatitis B serology showed positive anti-HBs and anti-HBc, a pattern consistent with prior exposure or resolved infection, without clinical or biochemical evidence of active hepatitis.

A contrast-enhanced computed tomography scan of the chest, abdomen, and pelvis showed a left renal mass measuring 5 × 5 × 5.2 cm, lobulated, with heterogeneous enhancement and necrotic areas; no metastatic lesions were identified *(Fig. 1)*. Bone marrow aspirate and biopsy showed trilineage haematopoiesis, a decreased myeloid/erythroid ratio due to mild erythroid hyperplasia, and a preserved megakaryocytic series with precursors at different maturation stages, without dysmegakaryopoiesis or increased blasts. The peripheral smear confirmed severe thrombocytopenia, macroplatelets, and absence of



Figure 1. Contrast-enhanced abdominal computed tomography scan. Heterogeneous solid mass in the upper pole of the left kidney, measuring 5 × 5 × 5.2 cm, with lobulated and irregular borders and heterogeneous enhancement, without identifiable metastatic lesions.

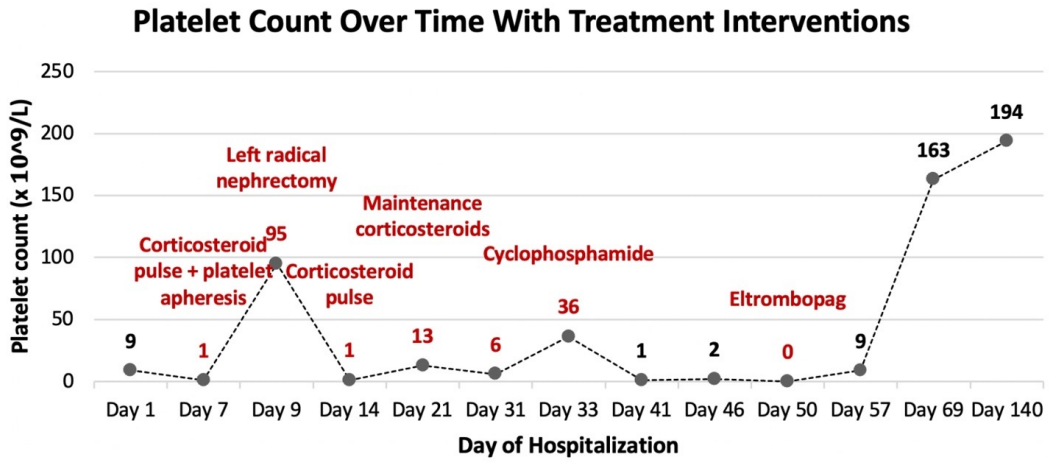


Figure 2. Platelet count during hospitalization and main therapeutic interventions. The platelet nadir on admission (5 ×10³/µl), the /persistence of severe- thrombocytopenia during the perioperative period despite corticosteroids, intravenous immunoglobulin, and nephrectomy, and the sustained ascending inflection following initiation of the thrombopoietin receptor agonist (eltrombopag), with progressive normalization by postoperative week 9, are shown.

Domain	Main results	Clinical interpretation
Initial blood count	Hb 8.5 g/dl (14.0–16.5); Platelets 5 ×10³µl (130–400); Leukocytes 13.63 ×10³/µl (4.0–11.0), with neutrophilia	Anaemia and profound thrombocytopenia at diagnosis.
Autoimmune haemolysis	Direct Coombs 4+ (IgG 3+, IgA 1+, IgM 1+, C3c 1+, C3d 3+); Total bilirubin 2.83 mg/dl (0.3–1.2); Indirect bilirubin 2.28 mg/dl; Haptoglobin 15 mg/dl (30–200); LDH 612 U/l (135–225)	Warm-antibody AIHA with complement activation.
Coagulation/consumption	INR and aPTT normal; Fibrinogen 189–229 mg/dl (200–400); D-dimer within normal range	No laboratory evidence of overt DIC.
Peripheral smear	Severe thrombocytopenia; Macroplatelets; No circulating blasts; Manual platelet count 23 ×10³/µl	True thrombocytopenia of peripheral origin.
Bone marrow/flow cytometry	Three cell lines present; Mild erythroid hyperplasia; Megakaryocytes present without dysplasia; No blasts or lymphoid clonality	No bone marrow failure, hematologic infiltration, or significant dysplasia.
Viral and autoimmune studies	HIV, HCV, and *H. pylori* negative; ANA and ENA non-reactive; HBV serology: anti-HBs and anti-HBc positive (resolved infection)	No active infectious or systemic autoimmune aetiology identified.
Renal neoplasm	Clear cell renal cell carcinoma; ISUP/WHO grade 2; 4.5 × 4 cm; pT1b; Negative margins	Localized, resected renal tumour.

Table 1. Relevant diagnostic findings.
Abbreviations: Hb, haemoglobin; AIHA, autoimmune haemolytic anaemia; LDH, lactate dehydrogenase; INR, international normalised ratio; aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; HIV, human immunodeficiency virus; HCV, hepatitis C virus; ANA, antinuclear antibodies; ENA, extractable nuclear antigen; HBV, hepatitis B virus; ISUP, International Society of Urological Pathology; WHO, World Health Organization.

circulating blasts, with a manual platelet count of 23 ×10³/µl. Bone marrow flow cytometry showed no pathologic myeloid blasts, B lymphoblasts, or clonal mature lymphoid population. These findings were consistent with peripheral thrombocytopenia associated with AIHA. Relevant diagnostic findings are listed in *Table 1*.

A diagnosis of secondary Evans syndrome (severe ITP with concurrent AIHA) associated with localized clear cell renal cell carcinoma was established. The patient received prednisone 60 mg/day; due to persistence of

extreme thrombocytopenia, pulses of dexamethasone and intravenous immunoglobulin were administered. Platelet transfusions were used as perioperative support given the need for nephrectomy. In view of the coexisting localized renal neoplasm and the presumed paraneoplastic component, surgical management of the tumour was prioritized.

Left radical nephrectomy was performed. Pathology confirmed clear cell renal cell carcinoma, International Society of Urological Pathology/ World Health Organization grade 2, 4.5 × 4 cm, located in the upper pole, without evident lymphovascular invasion; perirenal tissue, renal sinus, renal sinus vein, renal hilum, and ureteral margin were free of disease (pT1b). Severe thrombocytopenia persisted after surgery and additional courses of corticosteroids. Platelet antibody screening was positive without antigen specification; given its limited sensitivity and specificity, it was interpreted as a complementary finding only. Given therapeutic refractoriness, cyclophosphamide and subsequently eltrombopag, a thrombopoietin receptor agonist, were administered, with progressive platelet count increase and a sustained response during follow-up. *Figure 2* shows the platelet nadir during the first weeks of hospitalization, the maintenance of severe thrombocytopenia during the perioperative period, and the ascending inflection after TPO-RA initiation, with progressive normalization by postoperative week 9.

Secondary Evans syndrome (persistent immune thrombocytopenia and concurrent autoimmune haemolytic anaemia) associated with localized clear cell renal cell carcinoma (pT1b).

DISCUSSION

ITP is an acquired immune-mediated disorder defined by a platelet count below 100 $\times 10^9$/l, resulting from peripheral destruction and insufficient platelet production. Its diagnosis is clinical and one of exclusion, requiring the rule-out of pseudo thrombocytopenia, consumption, drugs, infection, hepatosplenic disease, and bone marrow pathology[1–3]. In the present case, thrombocytopenia was true and peripheral: peripheral smear with macroplatelets and a low manual count, megakaryocytes present without dysplasia, absence of blasts or lymphoid clonality on flow cytometry, and coagulation studies without evidence of overt disseminated intravascular coagulation. AIHA was documented by a 4+ direct Coombs with IgG and complement, indirect hyperbilirubinemia, low haptoglobin, and elevated lactate dehydrogenase. The concurrence of immune-mediated ITP and AIHA, in the absence of an identifiable systemic autoimmune, infectious, or lymphoproliferative cause, is consistent with Evans syndrome; the presence of an underlying neoplasm categorizes it as secondary Evans syndrome[5].

The pathophysiology of ITP involves antiplatelet autoantibodies, splenic phagocytosis, complement activation, regulatory T-cell dysfunction, and a predominance of Th1/Th17 responses. In addition, immune activation may promote platelet desialylation, with hepatic clearance through the Ashwell-Morell receptor, a mechanism that complements classical splenic destruction and contributes to persistent thrombocytopenia[1-4]. In secondary ITP, the trigger may be infectious, autoimmune, pharmacological, or neoplastic. Solid tumours are exceptional causes; in the classic review of paraneoplastic ITP by Krauth et al., cases associated with multiple tumour types were described, predominantly breast and lung cancer, with presentation before, simultaneous to, or after the oncologic diagnosis, and it was documented that autoimmune activity may persist for weeks or months following tumour control[4]. The association with renal cell carcinoma is rare and limited to isolated reports, so its recognition requires rigorous diagnostic exclusion.

A critical consideration in this case is the strength of the causal link between renal cell carcinoma and the immune cytopenias. We acknowledge that the persistence of thrombocytopenia for approximately 7 weeks following nephrectomy, and the platelet recovery coinciding with the introduction of TPO-RA rather than with surgery, do not allow direct causality to be established between tumour resection and hematologic resolution. A primary ITP coincident with an incidental renal cell carcinoma represents an alternative diagnosis that cannot be excluded with certainty. Nevertheless, several elements support the paraneoplastic interpretation: the simultaneous presentation of both entities, the absence of an alternative identifiable cause after extensive work-up, the coexistence of AIHA and ITP (configuring Evans syndrome, an unusual association in adult primary ITP), and the temporal pattern of immune persistence after tumour control described by Krauth et al. in other solid tumours[4]. This causal limitation is explicitly acknowledged and is one of the inherent challenges in reports of hematologic paraneoplastic phenomena associated with localized tumours.

Treatment is aimed at reducing bleeding risk, limiting toxicity, and achieving safe platelet counts. Corticosteroids are first-line therapy; short courses of prednisone or dexamethasone 40 mg/day for 4 days are accepted, avoiding prolonged exposure[6,7]. Intravenous immunoglobulin is reserved for rapid platelet elevation, clinically relevant bleeding, or perioperative preparation[6]. In persistent or refractory disease, rituximab and thrombopoietin receptor agonists are second-line alternatives[6,8,9]. In the present case, the response to corticosteroids and immunoglobulin was insufficient; TPO-RA was associated with progressive and sustained platelet recovery. Notably, the evidence regarding the use of TPO-RAs in ITP secondary to solid tumours is considerably more limited than in primary ITP and relies mainly on small series and case reports[9,10]. Our case provides additional clinical evidence on the utility of these agents in this specific scenario, particularly when immune activity persists after

surgical control of the primary tumour.

In summary, secondary Evans syndrome associated with localized clear cell renal cell carcinoma is an exceptional presentation. Recognition of this disorder requires rigorous diagnostic exclusion. Persistence of cytopenias following surgical tumour control does not rule out a paraneoplastic origin and may require therapeutic escalation. TPO-RAs may represent an effective option in this refractory setting, although evidence remains limited and further reports are needed to confirm their efficacy and safety profile in ITP secondary to solid tumours.

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