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Case Report

Autoimmune Haemolytic Anaemia Due to Cold Antibodies in a Renal Cancer Patient

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Keywords
Renal cancer · Autoimmune haemolytic anaemia · Cold antibodies · Paraneoplastic syndrome

Abstract
Autoimmune haemolytic anaemia (AIHA) is an acquired disorder in which antibodies are produced against self-erythrocyte antigens. We distinguish those produced by cold antibodies (IgM), which may be associated with lymphoproliferative syndromes, infectious diseases, other autoimmune phenomena, as well as drugs or solid tumours. We report a case of AIHA due to cold antibodies as a paraneoplastic syndrome (PNS) in a patient with metastatic renal carcinoma. A 67-year-old man with newly diagnosed stage IV renal carcinoma with hepatic, bone, and lymph node involvement was consulted for abdominal pain. Laboratory tests showed grade 4 anaemia (4.5 g/dL), with positive direct Coombs' test C3bC3d and agglutinated red blood cells in the blood smear. AIHA by cold antibodies was labelled as PNS in the context of the patient; therefore, blood transfusion as well as treatment of the underlying disease with tyrosine kinase inhibitors (sunitinib) were initiated, with subsequent clinical and analytical improvement. AIHA due to cold antibodies is a well-known PNS in lymphoproliferative disorders, although association with solid tumours, such as Kaposi's sarcoma and non-small-cell lung cancer have also been described in a small percentage. However, there are few reported cases of AIHA due to cold antibodies associated with renal carcinoma. Management with corticosteroids and immunosuppressors is effective in the majority of cases, but treatment of the underlying disease is critical.

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Introduction

Autoimmune haemolytic anaemia (AIHA) is an acquired haemolytic anaemia caused by the presence of antibodies directed against antigens of the patient's own red blood cells (named autoantibodies). The incidence is around 1–3 cases per 100,000 persons/year. AIHA may be mediated by IgG, IgM, or IgA autoantibodies. However, AIHAs due to warm antibodies are usually associated with IgG; on the contrary, AIHAs due to cold antibodies are correlated with IgM. In the latter case, the highest reaction occurs at 4°C, and in extreme cases, the agglutination may happen at 37°C. This autoantibody behaves as a complement-binding antibody (C3bC3d) with a high titre and a wide thermal range. This results mainly in intravascular haemolysis phenomena.

AIHA is mostly associated with secondary processes, such as lymphoproliferative syndromes [1], drugs [2], or infectious diseases, with solid tumours being a very rare cause [3]. The clinical behaviour depends on the degree of anaemia, and the laboratory test show reticulocytosis, elevated bilirubin, haptoglobin consumption, and increased lactate dehydrogenase (LDH). Since this is an autoimmune anaemia, the direct Coombs' test (polyspecific) is positive, and a monospecific Coombs' test should be performed to confirm complement activation (C3bC3d). In addition, titration of cold antibodies (or cryoagglutinins) is mandatory for diagnosis. Determinations of temperature range and titre are useful, as well as the presence of rouleaux-agglutinated red blood cells in the blood smear, which supports the diagnosis [4]. Polychromasia and circulating reticulocytes may also be seen in the laboratory test. The treatment is based on blood transfusions (when necessary, warm transfusions) or immunosuppressive drugs. However, management of the underlying disease is essential. We present here the exceptional case of AIHA due to cold antibodies as a paraneoplastic syndrome (PNS) in a patient with a recent diagnosis of clear-cell renal carcinoma.

Case Report

A 67-year-old male presented to the emergency department of our hospital with asthenia associated to colicky abdominal pain. The patient had recently been diagnosed (January 2020) with stage IV clear-cell renal-cell carcinoma due to hepatic, bone, and lymph node involvement (poor prognosis subgroup according to the International Metastatic Database Consortium [IMDC] criteria) (Fig. 1). The patient was awaiting the initiation of

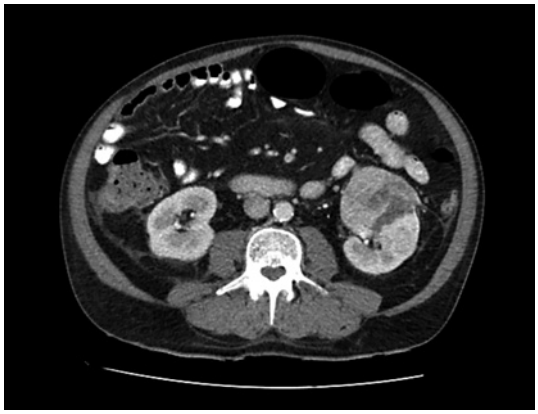

Fig. 1. Abdominal CT. Axial section. Diagnostic image showing a necrotic left renal mass suggestive of primary renal neoformation of approximately 8.2 cm with an associated adenopathic conglomerate. CT, computed tomography.

systemic treatment. On physical examination, the patient presented skin pallor with no other relevant findings of interest.

Complementary Tests

Laboratory tests showed a hypochromic-microcytic anaemia grade 4 (haemoglobin [Hb] of 4.5, 9.5 g/dL the previous week), with high erythrocyte distribution amplitude, reticulocytosis, and associated thrombocytosis, as well as increased total bilirubin levels of 2.60 mg/dL (conjugated bilirubin 2.48 mg/dL) and LDH of 340 U/L (Table 1). Imaging studies were performed; abdominal computed tomography ruled out active haemorrhage given the acute anaemia together with the abdominal pain (Fig. 1). Given the suspected diagnosis of haemolytic anaemia, a peripheral blood smear was performed in which anisopoikilocytosis, aggregate red blood cells in rouleaux, leucocytosis, and thrombocytosis were observed (Fig. 2). Likewise, in the immunohematological study, the direct Coombs test (polyspecific) was positive (+4). In the monospecific study, the result was also positive for anti-IgG (+2) and anti-C3bC3d (+4). A cryoagglutinin study was also performed, including titration and temperature range (4°C, 22°C, and 37°C), being conclusive of cold agglutinin disease, with high levels in the parameters analysed.

After this diagnosis, the patient was admitted to the hospital, and treatment with blood transfusion was started. During his time in hospital, other causes of AIHA were ruled out, such as the presence of an infectious process; negative blood cultures and negative microbiological analysis for cytomegalovirus, Epstein-Barr virus, herpes simplex virus, hepatitis (A, B, and C), rubella, HIV, varicella zoster, and erythrovirus B19 were obtained. We also excluded other possible aetiologies such as autoimmune diseases, as well as lymphoproliferative syndromes, being the definitive diagnosis of AIHA by cold antibodies as PNS secondary to metastatic renal-cell carcinoma. Treatment was started immediately with tyrosine kinase inhibitors (sunitinib) at a dose of 50 mg/24 h (4:2 schedule) as systemic treatment of his metastatic clear-cell renal-cell carcinoma was promptly started (nivolumab-ipilimumab, axitinib-pembrolizumab, or cabozantinib-nivolumab combinations were not funded at that time by the Spanish National Health System). After 4 days of treatment, the patient presented progressive clinical and analytical improvement (Table 1), with a rise in Hb levels. After 8 days of hospitalization and initiation of treatment with sunitinib, the patient was discharged from the hospital.

Clinical Judgement

AIHA due to cold antibodies as PNS in a patient with a recent diagnosis of metastatic clear-cell renal carcinoma.

Discussion

AIHA is a PNS that may be associated to lymphoproliferative disorders [1], including non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, although associations with solid tumours have also been described in a small percentage of cases [3]. Previous studies have shown that in patients with newly diagnosed of AIHA, around 5.7% have a solid underlying neoplasm [5]. However, cases of AIHA related to solid tumours represent a minimal percentage, and their association with solid tumours are unusual. In a series of 856 patients with AIHA, only 55 of them had non-haematologic malignancy (10% were ovarian tumours) [6]. In another study of 130 patients with cancer and AIHA, only 10 patients had solid tumours such as ovarian cancer, thymoma, or Kaposi's sarcoma [7]. AIHA as a PNS appears to occur more frequently in Kaposi's sarcoma and non-small cell

Table 1. Evolution of analytical parameters

Analytical value	Admission (day 0), February 21, 2020	February 24, 2020	February 26, 2020	February 27, 2020	Discharge (DÍA +7), February 28, 2020	March 03, 2020	Reference range
Haematology							
Hb, g/dL	**4.5**	6.9	6.4	7.8	8.9	8.2	13.0–18.8
Reticulocytes, %	3.4	2.6	3.1	–	–	–	0.5–1.5
Leucocytes, /μL	20,430	15,700	10,350	12,700	9,790	10,620	4,500–10,800
Neutrophils, /μL	19,400	13,200	8,230	10,700	7,840	8,800	1,460–6,500
Lymphocytes, /μL	1,110	1,370	1,370	1,460	1,410	1,380	1,200–3,500
Platelets, /μL	569,000	654,000	688,000	565,000	466,000	499,000	150,000–450,000
Biochemistry							
Total bilirubin, mg/dL	**2.60**	1.00	0.86	0.84	0.61	0.63	0.15–1.20
Conjugated bilirubin, mg/dL	2.48	–	–	–	–	–	–
LDH, U/L	340	237	284	302	309	411	135–225
Inmunoquímicam, UI/mL							
Erythropoietin	–	17.9	–	–	–	–	4.3–29.0
Protein, mg/dL							
Haptoglobin	–	**39.20**	–	–	–	–	30.00–200.00
Autoimmunity							
Anti-cyclic citrullinated cyclic peptide Ab, U/mL	–	50.2	–	–	–	–	0.0–5.0
ASMA: IgG	–	Negative	–	–	–	–	–
Anti-f actin Ab	–	22.9	–	–	–	–	0.0–20.0
AMA: IgG	–	Negative	–	–	–	–	–

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Table 1 (continued)

Analytical value	Admission (day 0), February 21, 2020	February 24, 2020	February 26, 2020	February 27, 2020	Discharge (DÍA +7), February 28, 2020	March 03, 2020	Reference range
Anti-M2 mitochondrial Ab: IgG	–	0.1	–	–	–	–	0.0–10.0
Anti-LKM Ab: IgG	–	Negative	–	–	–	–	–
ANCA	–	Negative	–	–	–	–	–
Anti-myeloperoxidase Ab: IgG	–	1.0	–	–	–	–	0.0–6.01
Anti-proteinase 3 Ab: IgG	–	1.0	–	–	–	–	0.0–5.01
ANA: IgG	–	Positive	–	–	–	–	–
Anti-DNA: IgG	–	3.5	–	–	–	–	0.0–15.01
Ana titration HEP-2	–	1/1,160	–	–	–	–	–
Anti-ENA Ab screening	–	Negative	–	–	–	–	–
aCL IgG	–	4.50	–	–	–	–	0.0–10.0
Anti-B2 glycoprotein I Ab: IgG	–	2.60	–	–	–	–	0.0–10.0

Bold: The data of decreased hemoglobin, increased bilirubin and decreased haptoglobin are indicative of a diagnosis of hemolytic anemia. ASMA, anti-smooth muscle Ab; AMA, anti-mitochondrial Ab; aCL, anti-cardiolipin; ANA, anti-nuclear Ab.

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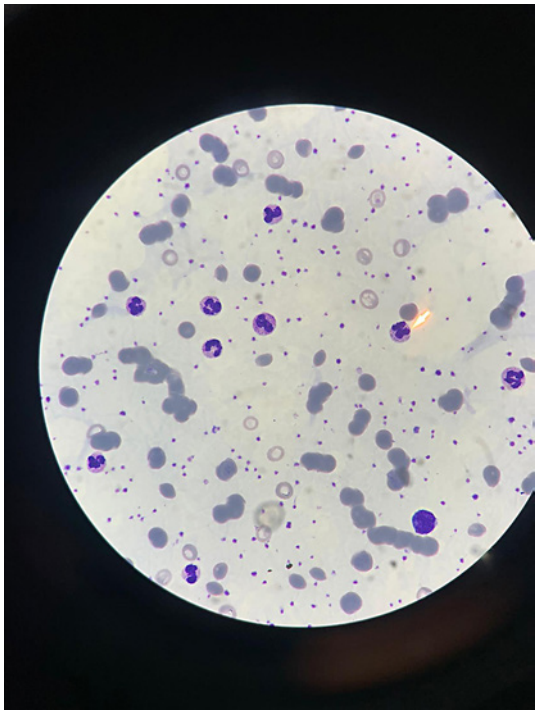

Fig. 2. Peripheral blood smear: aggregate red blood cells in rouleaux (red arrow), anisopoikilocytosis, neutrophilia with reinforcement of granulation, and real thrombocytosis.

lung cancer. Other tumours including seminomas, prostate, ovarian, and breast are rarely associated with this entity [8]. Renal neoplasms are even less frequently associated with haematologic SPNs. AIHA has been described as a PNS of renal tumours with data of severe anaemia with significant morbidity and mortality [9, 10]. AIHA may be caused by warm or cold autoantibodies [11], but in solid tumours, approximately 2/3 are caused by warm antibodies. Most cases of AIHA associated with malignant solid tumours occur within 6 months of cancer diagnosis, as is the case presented here. The clinical and analytical presentation of AIHA is based on signs of anaemia, jaundice, and a positive direct Coombs' test for anti-C3bC3d and negative or weakly positive for anti-IgG [12], confirming the diagnosis [13] of cold antibody AIHA. Anaemia was the main clinical sign in our patient, with an Hb value of 4.5 g/dL on the day of admission, and other laboratory tests were also consistent with the described picture.

According to the literature, autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, or scleroderma [14] can be the cause of AIHA. This entity has also been described in patients with viral infectious diseases such as mycoplasma pneumoniae, mononucleosis, syphilis, or taking antimicrobial drugs such as cephalosporins [2]. In our patient, all the described causes were ruled out. Taking into account the laboratory findings and the recent diagnosis of cancer, the AIHA picture was labelled as PNS in a patient with metastatic renal carcinoma.

Treatment with corticosteroids and immunosuppressants is effective in a variable percentage of cases [15, 16], and warmer blood transfusions are also useful. Removal of the tumour and/or splenectomy may improve the haematologic alterations. However, the definitive management is the treatment of the underlying disease, in this case, the metastatic renal-cell carcinoma. In our patient, slight improvement was observed after starting blood warmer transfusions on the day of admission. Within days of being admitted, after starting the treatment with sunitinib, we observed an improvement in the laboratory test: decrease in bilirubin, LDH, and leucocyte levels and an increase in red series levels (Table 1). This could

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be due to the decrease in tumour antigenic load with the tyrosine kinase-targeted therapy; tyrosine kinase inhibitors (sunitinib).

Conclusion

We present an unusual case of AIHA due to cold antibodies as PNS of metastatic renal carcinoma. In patients with a diagnosis of clear-cell renal carcinoma together with acute haematological alterations, it is important to rule out PNSs, such as the case described here. Treatment of the underlying disease is the primary approach.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. All the authors of this report are greatly obliged to the Editorial Board for the publication of this report. The study is exempt from Ethics Committee approval since it is a case report at the University Hospital of Salamanca.

Conflict of Interest Statement

Eduardo Terán Brage has no relationship to disclose. Marta Fonseca Santos has no relationship to disclose. Rebeca Lozano Mejorada declares speaker fees from Roche, Astellas, Janssen Bayer, and Sanofi and travel support from Roche, Janssen, IPSEN, Astellas, MSD, and Merck. Rocío García Domínguez declares speaker fees from IPSEN and BMS and travel support from Roche, IPSEN, and Pfizer. Alejandro Olivares Hernández has no relationship to disclose. Arantzazu Amores Martín has no relationship to disclose. Rosario Vidal Tocino declares speaker fees from Amgen, Merck, Sanofi, Servier, Bristol-MS, and Roche and educational and scientific activities and travel support from Amgen, Roche, Lilly, Sanofi, Bristol-MS, and Servier. Emilio Fonseca Sánchez has no relationship to disclose.

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Author Contributions

Eduardo Terán Brage was responsible for literature review, data collection, and manuscript writing. Marta Fonseca Santos reviewed the manuscript proposal. Rebeca Lozano Mejorada participated in technical editing of the manuscript. Alejandro Olivares Hernández collaborated in the performance of complementary tests that supported the definitive diagnosis. Arantzazu Amores Martín cared for the patient during the treatment. Rosario Vidal Tocino was responsible for the supervision and administration of the project. Rocío García Domínguez was responsible for the administration of the article once it has been written. Emilio Fonseca Sánchez contributed to manuscript review before submission and approved the final version.

Data Availability Statement

Data sets used and analysed during the present study are available from the corresponding author upon reasonable request to safeguard the confidentiality of the patient's clinical data. Legal entity responsible for the study: all the authors.

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