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Case Report

Autoimmune Haemolytic Anaemia Associated with Testicular Non-seminomatous Germ Cell Tumour (NSGCT): A Unique Paraneoplastic Presentation

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ABSTRACT

Paraneoplastic syndrome (PNS) is the rare manifestation of malignancy which presents as remote systemic features unrelated to direct tumour involvement. Often PNS can be the only presenting symptom of the cancer and may warrant search for underlying malignancy. Immune response against malignant cells sometimes cross reacts and destroys the normal cells. PNS can manifest at any point of time in course of malignancy, either it may presage diagnosis, or at relapse settings. Successful treatment of the malignancy is the key in managing PNS. Autoimmune haemolytic anaemia (AIHA) is a common presentation of haematological malignancy, but rarely reported with malignant solid tumours. We, hereby, illustrate a rare association of AIHA as PNS in a case of testicular non-seminomatous germ cell tumour and its management along with review of literature. To the best of our knowledge, this is the first such a case to be reported in the literature.

Keywords: Non-seminomatous germ cell tumour, Autoimmune haemolytic anaemia, Paraneoplastic syndrome, Testicular tumour, Haemolytic anaemia

INTRODUCTION

Paraneoplastic syndromes (PNSs) are relatively rare and often an interesting systemic manifestation of malignancy.[1] PNS is remote clinical or biochemical effects triggered by altered immune responses to neoplasm, not explained by the local extension or mass effect.[1,2] PNS may presage the diagnosis or develop anytime during the course of malignancy.[1] Depending on the organ systems affected, PNS may be classified as neurological, endocrine, mucocutaneous and/or haematological.

Anaemia is a common complication seen in patients with malignancy and is associated with increased morbidity, poor tolerance to treatment and worse clinical outcomes.[3] Aetiology of anaemia of malignancy is multifactorial such as nutritional, anaemia of chronic disease, drug induced, direct involvement of bone marrow, blood loss and haemolytic anaemia. Identification of the underlying cause of anaemia and appropriate management impacts clinical outcomes. Autoimmune haemolytic anaemia (AIHA) as PNS is commonly seen with haematological malignancies, but such association with solid malignancies particularly like testicular tumours is very rare.[4] Here, we discuss a clinical profile and management of paraneoplastic autoimmune haemolytic anaemia in a patient with testicular non-seminomatous germ cell tumour (NSGCT) and review of literature.

Here, we illustrate a unique paraneoplastic presentation of AIHA in association with testicular NSGCT. Such association needs to be verified after excluding other more common aetiologies.

CASE REPORT

A 37-year-old young male patient with no comorbidities presented with complaints of swelling and ulcer on the right side of scrotum and radiating pain along right lower back to thigh. He also complained of fatigue and breathlessness on exertion limiting his day to day activities. General physical examination revealed pallor, tachypnoea, tachycardia, pedal oedema and Eastern Cooperative Oncology Group performance status of 3. Local examination confirmed right testicular swelling with ulcerated lesion over the right side of the scrotum. Rest of the systemic examinations were normal. PET CT scan showed metabolically enhancing right testicular mass lesion, multiple brain parenchymal, hepatic, right adrenal, pancreatic and bone lesions with enlarged para-aortic lymph nodes, as shown in [Figure 1]. MRI brain confirmed multiple ring enhancing space-occupying lesions in the brain. USG-guided biopsy with immunochemistry from liver lesions revealed atypical tumour cells positive for SALL4, OCT 3/4, CK, CD30 and negative for beta-HCG and GLYPICAN 3, suggestive of metastatic germ cell tumour, predominantly embryonal type, as shown in [Figure 2]. Tumour markers at baseline were, Alpha-fetoprotein (AFP) of 1330 ng/mL, beta-Human Chorionic gonadotropin of 3755 mIU/mL and Lactate Dehydrogenase (LDH) of 1140 IU/L. Based on imaging findings, tumour markers and histopathology the tumour was staged as stage IIIC, poor risk testicular NSGCT according to International Germ Cell Cancer Collaborative Group risk classification. Baseline blood parameters, as shown in [Table 1], revealed a haemoglobin level of 5.7 g/dL, white blood cell count of 27200/µL, platelet count of 376 × 103/µL, mean corpuscular volume of 74 fl and a corrected reticulocyte count of 4.2%. Peripheral smear showed normocytic normochromic anaemia with moderate anisopoikilocytosis, marked polychromasia with spherocytosis and nucleated red blood cells, fair number of microcytes and few tear drop cells. WBC series show neutrophilia with the left side shift and platelets were adequate, morphologically normal. Biochemistry panel showed serum total and direct bilirubin of 3.2 mg/dl (0.4–1.3 mg/dL) and 0.8 mg/dl, serum lactate dehydrogenase of 680 IU/L (240–460 IU/L) and vitamin B12, 369 pg/mL (225–1100 pg/mL) and direct Coombs test was positive for immunoglobulin G, CD 3a. Serum protein electrophoresis showed no abnormal monoclonal band spike.

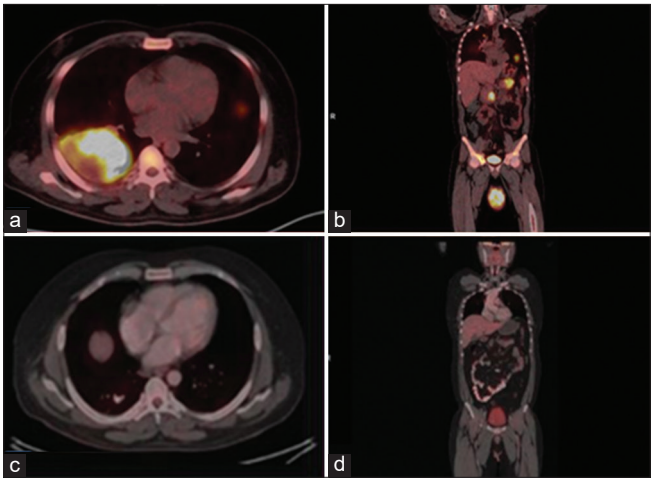

Figure 1: PET-CT at diagnosis (a and b) showing metabolically enhancing right testicular mass lesion, right adrenal, pancreatic, bone lesions with enlarged para-aortic lymph nodes and following three cycles of chemotherapy (c and d) showing metabolic resolution all the lesions.

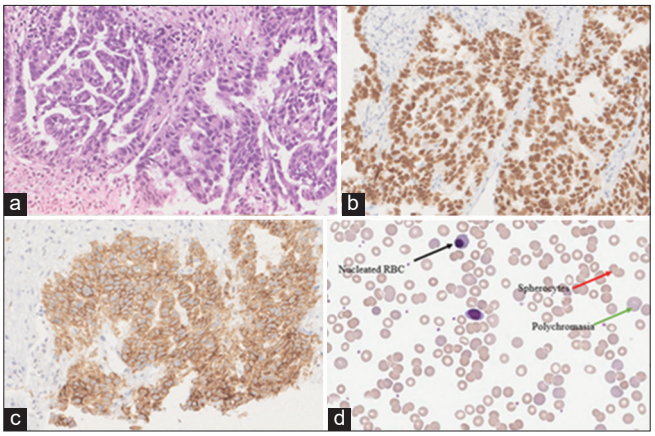

Figure 2: (a) H&E stained slides under ×20, tumour cells in glands and papillae, have moderate eosinophilic cytoplasm, moderately pleomorphic vesicular nuclei with frequent mitosis. (b and c) tumour cells with immuno-histochemistry studies, showed SALL 4 positivity (b) and CD 30 positivity (c and d) showing peripheral smear suggestive of haemolysis.

Management and patient course

After confirming the diagnosis of AIHA, the patient was started on corticosteroid, Tab Prednisolone 1 mg/kg once daily per orally after meals. Baseline haemoglobin was 5.7 g/dL at presentation. Despite initiation of steroids, the patient required repeated weekly blood transfusions in the first 2 months after diagnosis. The patient received palliative radiotherapy to the brain and lumbar vertebra for symptomatic brain and bony metastasis at presentation. In view of extensive disease at presentation and poor PS orchiectomy was deferred and started with chemotherapy on the 4th week of diagnosis. Chemotherapy included a 21 day cycle of Bleomycin, Etoposide and Cisplatin (BEP)-based regimen. Haemoglobin consecutively started improving significantly with the chemotherapy cycles and by the end of two cycles of chemotherapy, his transfusion

Table 1: Baseline lab parameters.

	On admission	Reference range
White cell count (per µl)	27200	4000–11000
Haemoglobin (g/dl)	5.7	12.0–18.0 (men)
Haematocrit (%)	19.0	35.0–54.0
Red cell count (per pl)	2.55	4.5–6.5
Mean corpuscular volume (fl)	74.0	76.0-96.0
Platelet count (per µl)	3,76,000	150,000–450,000
Differential count (%)		
Neutrophils	85	40–75
Lymphocytes	10	20–45
Monocytes	2	01–08
Basophils	0	00–01
Eosinophils	2	01–06
Sodium (mmol/l)	139	135–145
Potassium (mmol/l)	4.5	3.5–5.5
Chloride (mmol/l)	103	95–110
AFP (ng/ml)	920	<10
Blood urea nitrogen (mg/dl)	34	6–20
Creatinine (mg/dl)	2.84	0.7–1.4
Calcium (mg/dl)	7.0	8.5–10.5
Total protein (g/dl)	7.5	6.4–8.2
Albumin (g/dl)	2.41	3.6–5.6
Aspartate aminotransferase (U/litre)	41.90	0–40
Alanine aminotransferase (U/litre)	13.97	0–37
Alkaline phosphatase (U/litre)	344.6	108–306
Total bilirubin (U/litre)	3.2	0.0–2.0
Conjugated bilirubin (U/litre)	0.8	0.0–0.2
Lactate dehydrogenase (U/litre)	614	85–240
M spike (g/dl)	Not seen	
Reticulocyte count (%)	7.9	0.5–2.5
Prothrombin time (seconds)	16	12.0–15.0
International normalised ratio (seconds)	1.1	
Activated prothrombin thromboplastin time (seconds)	66.5	30.0
Folic acid (ng/ml)	4.8	4.0–18.0
Vitamin B12 (ng/l)	669	193–986
Iron level (µg/dl)	96	65–175
Transferrin (mg/dl)	191	200–360
Saturation (%)	20	20–44
Ferritin (µg/l)	93	5–244
ANA	Negative	

AFP: Alpha-fetoprotein

requirements stopped. Haemoglobin was improved to 9.7 by 3 weeks after the completion of chemotherapy and corticosteroid dose was tapered gradually, suggesting diagnosis of malignancy-related AIHA-PNS. Subsequently, he underwent right high inguinal orchiectomy with scrotum ectomy, as the scrotum was also involved at presentation. After that, he also underwent liver segmentectomy and right video-assisted transthoracic surgery-guided non-anatomical pulmonary wedge metastasectomy. Post-surgery AFP 3.25 ng/mL and HCG of <2.39 mIU/mL as shown in the Table 2. The patient is on regular follow-up and is doing fairly well with no post-treatment sequelae at 1 year follow-up with haemoglobin of 13 and no evidence of disease recurrence.

DISCUSSION

This is a rare and interesting case of warm antibody AIHA associated with widely metastatic NSGCT. AIHA is commonly seen in patients with haematological malignancies.[5] However, an association between AIHA and malignant solid cancers is less commonly reported, with a notably rare occurrence in NSGCT.[2,6] In 2016, Nenova *et al*. reported, only 14 (1.29%) out of the 1083 patients with solid tumours were associated with autoimmune PNSs and only three had AIHA.[6] Joe *et al*. compiled 52 case reports of AIHA associated with solid malignancies, commonly, associated solid malignancies are renal cell carcinoma and Kaposi sarcoma and only three cases were associated with testicular tumours.

The pathophysiology of haemolysis in PNS-AIHA is said to be related to the destruction of RBC by cross-reacting antibodies formed against the tumour itself.[1,5] Alternatively, the tumour may release the substance which alters the RBC membrane and makes it antigenic. To label AIHA as PNS, an underlying malignancy must be present and the diagnosis of AIHA must be made using Coombs test and presence of anti-erythrocyte antibodies, as seen in our case.[2,6] In our case, patient peripheral smear, indirect hyperbilirubinemia, increased reticulocyte count, LDH, with positive direct Coombs test for immunoglobulin G and CD 3a in the background of NSGCT suggest AIHA as PNS.

The therapeutic options for AIHA management are corticosteroids, splenectomy, rituximab and thereafter any of the immunosuppressive drugs.[5,7,8] Management of AIHA associated with solid malignancies is not well defined, is often refractory to steroids and resolves rapidly following treatment directed at underlying malignancy such as surgical resection or chemotherapy.[2,9] In our case despite steroids, there was minimal improvement in anaemia. Management of testicular tumours involves upfront high inguinal orchiectomy followed by chemotherapy with BEP.[10] We treated our patient with BEP-based regimen upfront due to

Table 2: Correlation of tumour markers and markers of haemolytic anaemia during disease course.

	At diagnosis	After 1st cycle of chemotherapy	After completion of chemotherapy	After completion of treatment
AFP (<10.0 ng/ml)	1330	18.5	2.42	4.09
BHCG (mIU/ml)	3755	4.75	<2.39	<2.39
LDH (240–460 U/L)	1140	377	248	148
Haemoglobin (g/dl)	5.7	7.6	9.7	10.7
Reticulocyte count	7.9%	4.8%	2%	2%
Bilirubin (mg/dl)	3.2	2.6	1.4	1.2

AFP: Alpha-fetoprotein, LDH: Lactate dehydrogenase

poor general condition, for which he responded well and resolution of anaemia paralleled resolution of cancer.

CONCLUSION

AIHA is a well-known paraneoplastic phenomenon in lymphoproliferative disorders, but an association between AIHA and malignant solid cancers is less commonly reported, with a notably rare occurrence in NSGCT. AIHA in solid malignancies is often refractory to steroid therapy and treatment of underlying malignancy is crucial for the management.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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