Angio-Immunoblastic T Cell Lymphoma Presenting With Vasculitis and Hypercalcemia

Rudrajit Paul[1], Parul Bagri[2], Tushar K Bandyopadhyay[3], Jayanti Ray[4]

ABSTRACT

Angioimmunoblastic T Cell Lymphoma (ATCL) is a rare variety of Non-Hodgkin's lymphoma. It often presents with atypical signs like skin rash or arthritis and thus, the diagnosis is often delayed. We here present a case of ATCL that presented with cerebral vasculitis like features, followed by digital gangrene and then hypercalcemia. At first the lymph node biopsies were negative and only much later, repeat biopsy proved the diagnosis. In microscopy, effacement of paracortical area with infiltration of blood vessels was found. The patient responded to chemotherapy with resolution of some of the symptoms. The case highlights the atypical presentation of haematological malignancies and the need for follow up for proper diagnosis. Such a presentation has never been reported from Indian subcontinent.

Key words: Gangrene, Hypercalcemia , Non-Hodgkin's Lymphoma, T-cell lymphoma, Vasculitis

[1,3] Assistant Professor, [2]Resident, [4] RMO-Cum-Clinical Tutor

Department of Medicine, Medical College, Kolkata, India

Corresponding Author mail: docr89@gmail.com

Conflict of interest: none Financial support: none

Previous presentation: none Consent: taken Ethical permission: taken

INTRODUCTION

Angio-Immunoblastic T cell lymphoma (ATCL) is a peripheral T cell clonal disorder, a sub class of non Hodgkin's lymphoma (NHL), with many systemic features[1]. The exact aetiology of this relatively rare lymphoma is not known, but some authors believe that it may be related to latent infections[2]. Follicular helper T cells reacting to repeated infections, especially viral infections, may transform into a highly proliferative clone of malignant cells[1]. However, the clinical course is variable and treatment is also not fully validated.

ATCL is associated with many systemic features like fever, rash or arthritis[3]. These systemic features may precede the appearance of other features of lymphoma. These non-specific presentations make early diagnosis of the disease difficult. Hence, proper follow up is needed in these cases.

We here report a case of ATCL presenting first with vasculitic features and acute

onset Hypercalcemia. Such presentation is rarely reported in literature. This case will sensitize the clinicians to atypical presentations of haematological malignancy in general and T cell lymphomas in particular. Especially, a patient presenting with recurrent systemic features which fail to resolve with empirical therapy needs further evaluation.

CASE REPORT

A non-diabetic, non-hypertensive 38 year old female presented with low grade fever for 2 months along with loss of weight and anorexia. However, within seven days, the fever became high grade, along with severe headache and generalized tonic-clonic seizures. On admission, she was found to have mild pallor and bilateral papilledema. Cerebrospinal fluid (CSF) analysis showed protein of 158mg/dl, glucose 24mg/dl and cell count of 410 cells/mm^3; out of which 85% were mononuclear cells. The CSF was negative for bacteria by Gram stain and also PCR studies for M.Tb and HSV were negative. The blood tests were all normal, except for hemoglobin of 6 g% and an ESR of 80 mm in 1st hour. Anti nuclear factor (ANF) was positive in 1:80 dilution. MRI brain (Figure 1) was suggestive of inflammatory lesions in the right parieto-occipital region and an acute lacunar infarct in right thalamic region. She was provisionally diagnosed as primary CNS vasculitis and discharged with anti-epileptic drugs and steroids.

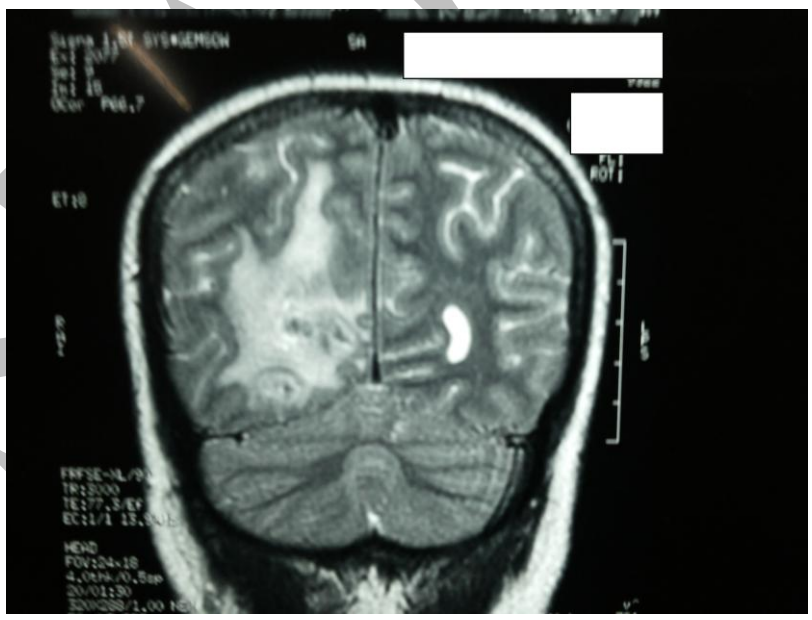

Figure 1: Figure of the MRI scan (T2 sequence) coronal view showing subcortical hyper intensity in right parietal area

The patient was apparently well for 4 months when she developed bilateral digital gangrene of upper limbs along with maculopapular erythematous pruritic rash

all over the body (Figure 2). There was no history of photosensitivity, oral ulcer, malar rash, Raynaud's phenomena, respiratory complaints, chest pain or pedal edema.

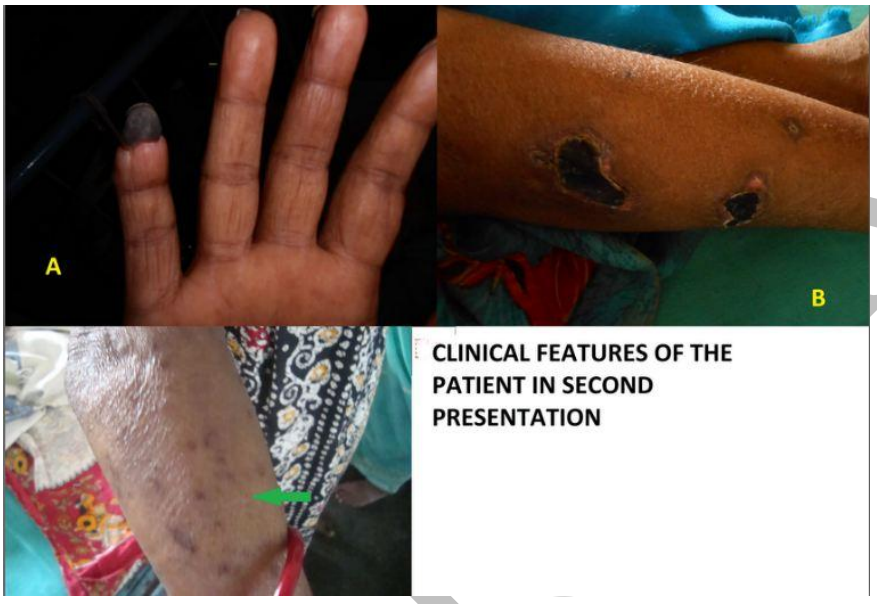

Figure 2: Figure showing the digital gangrene (A), necrotic skin lesions (B) and macular rash in upper limbs (Green arrow)

On examination, all the peripheral pulses were equal and palpable; there were several rubbery non tender lymph nodes. Blood tests revealed serum ANA, anti-ds DNA, c-ANCA, p-ANCA, anti-phospholipid antibody, cryoglobulin, complement C3 and C4 levels to be normal. Renal profile was also normal. Chest and abdominal imaging was non-specific and biopsy from the skin lesions only showed areas of necrosis. She was found to have raised serum Globulin of 8.9g/dl. Serum protein electrophoresis showed polyclonal gamma globulin band and bone marrow examination was also normal. Lymph node biopsy showed paracortical hyperplasia without any evidence of lymphoma, granuloma or vasculitis. She was again discharged on oral steroids with diagnosis of possible systemic vasculitis.

Two months later she again presented with sudden onset altered sensorium with delirium. There was no preceding history of fever, diarrhoea or vomiting. On examination she had moderate degree of pallor with generalised lymphadenopathy and evidence of dehydration. There was no neck rigidity. On laboratory testing, her hemoglobin was found to be 5.7gm % with a reticulocyte count of 6.5%. Her platelet count was 35,000/cumm. The total and differential leukocyte counts were normal.

We later found Direct Coomb's test to be positive and peripheral blood smear also showed presence of fragmented RBCs and schistocytes. Serology for HIV and EBV were negative. Globulin was persistently high (9 gm/dl). Serum electrolytes were normal except for raised calcium of 13 mg/dl (Albumin 3.1 gm/dl). CSF study was normal. MRI brain showed resolution of the earlier lesions. Liver function test was also normal; serum LDH was 1600 IU/L. serum vitamin D level was normal and PTH levels were low. She was managed with prompt hydration, i.v. dexamethasone and forced diuresis to which she responded quickly. On consultation with haematology department, a repeat biopsy from axillary lymph node was done. Lymph node biopsy this time was suggestive of lymphomatous proliferation of cells, effacement of normal nodal architecture, with infiltration of cells around blood vessels in paracortical area (Figure 3).

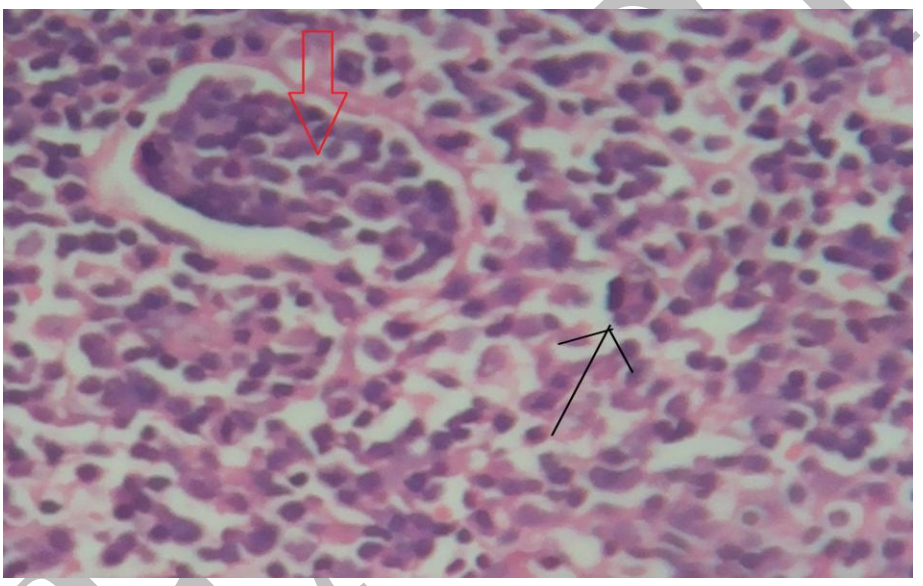

Figure 3: Photomicrograph of the lymph node biopsy showing mitotic lymphoma cells (Black arrow) and invasion of blood vessels (Red open arrow)

Arborizing post capillary venules lined by plump endothelial cells were seen. In view of the patients clinical presentation a diagnosis of Angio-Immunoblastic lymphoma was made. Immunohistochemistry was positive for CD3 and CD5 in 90% of the cells, CD4 was positive in 85% of cells and CD10 in 80% of the cells. CD 20 was negative. Staining for Tdt was negative. Thus, the final diagnosis was peripheral T cell angioimmunoblastic lymphoma. There was no evidence of bone marrow infiltration in marrow aspiration studies.

After stabilization, chemotherapy was started with cyclophosphamide, vincristine and prednisolone. The lymphadenopathy decreased and there were no further vasculitic signs. She was later transferred to oncology wards.

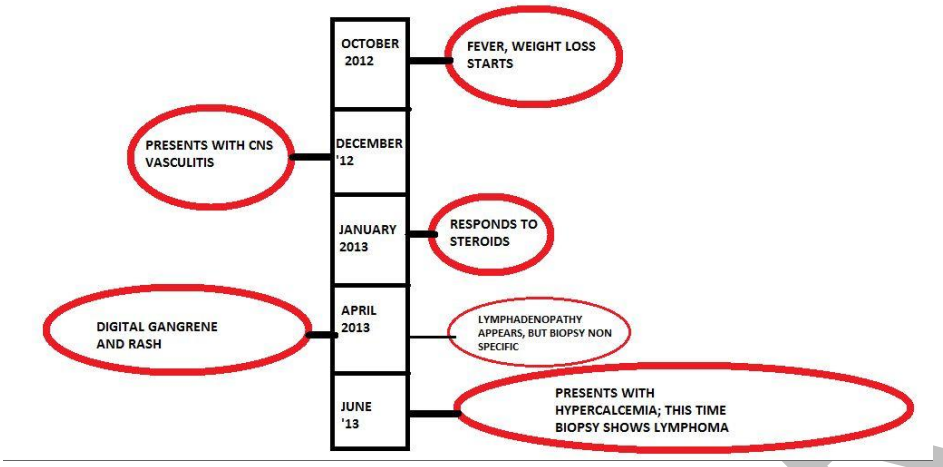

Figure 4: Schematic diagram of temporal profile of the patient

DISCUSSION

Vasculitis or rheumatologic manifestations of haematological malignancies are rarely reported[3]. However, when present, the features can mimic diseases like rheumatoid arthritis; only appearance of definite signs like significant lymphadenopathy in later stage can reveal the underlying aetiology[3]. ATCL is a disease whose natural history is still poorly known[4]. The course is unpredictable, but often found to be aggressive[4]. It is a disease of older males; however our patient presented at 38 years of age.

The following table depicts some of the available literature on rheumatological manifestations of ATCL: -

Author/year	Country	Manifestations	Fate of rheumatological disorder
Tsochatzis E et al, 2005[3]	Greece	symmetric inflammatory polyarthritis and skin nodules resembling rheumatoid arthritis	Responded to prednisolone
Jung et al, 2013[5]	Korea	Exacerbation of Ankylosing Spondylitis	N.A.
Notas et al, 2009[6]	Greece	Polyarthritis	Responded to methotrexate and steroids
Endo et al, 2011[7]	Japan	LCV,pemphigoid	N.A.
Sugaya et al, 2001[8]	Japan	LCV	N.A.
Ambrosio et al, 2012[9]	Italy	Polyarteritis nodosa	Responded to chemotherapy

*N.A.: not available; LCV: leukocytoclastic vasculitis

So, as seen in this table, the manifestations of ATCL can be varied. Our patient presented with digital gangrene and skin rash, along with CNS vasculitis. Digital gangrene has been rarely reported in lymphoma[10]. The cause of gangrene is thrombosis of vessels, probably secondary to a vasculitic process[10]. Definite therapy is still not defined.

CNS vasculitis is also rarely reported in cases of lymphoma. A case reported from USA in 2002 showed imaging characteristics of brain similar to ours, in a case of poorly differentiated lymphoma[11]. The malignancy in their case was ALCL, also referred to as intravascular lymphomatosis or malignant angioendotheliomatosis, a lymphoma with behaviour similar to ATCL. Definitive diagnosis of CNS vasculitis is only possible by brain biopsy, which is technically difficult to do ante mortem. Hence, imaging characters are enough to start steroid therapy and the norm is to follow up for response. Our patient responded well to steroid therapy.

Thus, our patient had two rare characteristics: digital gangrene and CNS vasculitis.

Our patient also presented with acute Hypercalcemia. Hypercalcemia occurs in lymphoma due to excess extra-renal vitamin D, synthesized not by lymphoma cells, but by reactive macrophages in tissues[12]. This mainly occurs in B cell lymphomas[12]. Very rarely, T cell lymphomas have been found to cause hypercalcemia. Mostly these are associated with HTLV-1 infection[13]. However, the mechanism of hypercalcemia in T cell lymphoma is different. Here, excess osteoclast activation and misbalance of prostaglandins are said to cause high serum calcium by bone resorption[14]. In our case, the serum vitamin D levels were normal. However, ATCL is very rarely reported to cause hypercalcemia. Our case presented with hypercalcemia in the emergency. This is probably the first report of such presentation of ATCL.

Our case highlights the rare and varied presentations of lymphoma. Unconsciousness in a lymphoma patient can be due to electrolyte disturbance, infection, CNS spread of the disease or, as in our case, CNS vasculitic insult. Hence, clinicians need to be aware of these systemic presentations of haematological malignancies in order to identify the underlying disease without delay.

REFERENCES

1. Frizzera G, Moran EM, Rappaport H. Angio-immunoblastic lymphadenopathy with dysproteinaemia. Lancet 1974;1:1070-3
2. Hawley RC, Cankovic M, Zarbo RJ. Angioimmunoblastic T-cell lymphoma with supervening Epstein-Barr virus-associated large B-cell lymphoma. Arch Pathol Lab Med. 2006;130:1707-11
3. Tsochatzis E, Vassilopoulos D, Deutsch M, Filiotou A, Tasidou A, Archimandritis AJ. Angioimmunoblastic T-cell lymphoma-associated arthritis: case

report and literature review. J Clin Rheumatol. 2005 ;11:326-8

4. Rodriguez-Justo M, Attygalle AD, Munson P, Roncador G, Marafioti T, Piris MA. Mod Pathol. 2009 ;22:753-61
5. Jung KH, Lim MJ, Kwon SR, Joo KW, Yi HG, Choi SJ, Park W. Angioimmunoblastic T cell lymphoma in an ankylosing spondylitis patient treated with etanercept. Mod Rheumatol. 2013 ;23:817-22
6. Notas G, Xylouri I, Kritikos H, Stavroulaki E, Roditakis G, Boumpas D. A rare case of angioimmunoblastic T-cell lymphoma presenting with fever and late polyarthritis. Rheumatology 2009;48:860–2
7. Endo Y, Tsuji M, Shirase T, Fukuda S, Hashimoto T, Miyachi Y et al. Angioimmunoblastic T-cell lymphoma presenting with both IgA-related leukocytoclastic vasculitis and mucous membrane pemphigoid. Eur J Dermatol. 2011;21:274-6
8. Sugaya M, Nakamura K, Asahina A, Tamaki K. Leukocytoclastic vasculitis with IgA deposits in angioimmunoblastic T cell lymphoma. J Dermatol. 2001 ;28:32-7
9. Ambrosio MR, Rocca BJ, Ginori A, Onorati M, Fabbri A, Carmellini M et al. Renal infarction due to polyarteritis nodosa in a patient with angioimmunoblastic T-cell lymphoma: a case report and a brief review of the literature. Diagnostic Pathology 2012;7: 50
10. Setoyama M, Yamamoto S, Kanzaki T. Adult T-cell leukemia/lymphoma presenting with digital gangrene. Dermatology. 1997;195:150-2
11. Song DK, Boulis NM, McKeever PE, Quint DJ. Angiotropic large cell lymphoma with imaging characteristics of CNS vasculitis. Am J Neuroradiol. 2002 ;23:239-42
12. Hewison M, Kantorovich V, Liker HR, Van Herle AJ, Cohan P, Zehnder D et al . Vitamin D-mediated hypercalcemia in lymphoma: evidence for hormone production by tumor-adjacent macrophages. J Bone Miner Res. 2003 ;18:579-82
13. Peter SA, Cervantes JF. Hypercalcemia associated with adult T-cell leukemia/lymphoma (ATL). J Natl Med Assoc. 1995; 87: 746–8
14. Grossman B, Schechter GP, Horton JE, Pierce L, Jaffe E, Wahl L. Hypercalcemia associated with T-cell lymphoma-leukemia. Am J Clin Pathol. 1981;75:149-55