

Case Report

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Immune Thrombocytopenic Purpura Following Acute Lymphoblastic Leukemia in Remission

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Abstract

This is a case report of a 19 year old male undergraduate with a background diagnosis of polycystic kidney and hypertension. Two years thereafter, he was diagnosed to have ALL L1 morphology which responded to induction chemotherapy using Vincristine and Prednisolone (V+P). He later proceeded to India where the same diagnosis was confirmed and molecular study pointed to standard risks ALL. Following successful Induction Remission and Consolidated therapy, he was sent to us to follow up his maintenance therapy. Patient defaulted severally. He represented with severe thrombocytopenia and thrombocytopenic bleeding with blood film and marrow being devoid of blasts but rather marrow showed numerous smooth, non-budding, cytoplasmic basophilic megakaryocytes in keeping with ITP. He responded rapidly to steroid therapy. Patient remains stable as at now after 3 months of steroid therapy. ITP following ALL in remission is an uncommon occurrence, hence this report.

Keywords: ALL; ITP; Chemotherapy; Bleeding

Abbreviations: Immune Thrombocytopenic Purpura (ITP); Acute Lymphoblastic Leukemia (ALL); Chronic Lymphocytic Leukemia (CLL); Systemic Lupus Erythematosus (SLE); Acute Myeloid Leukemia (AML)

Introduction

Immune Thrombocytopenic Purpura (ITP) is known to be associated with an abnormal autoantibody, usually immunoglobulin G (IgG) with specificity for GPIIb/IIIa and GPIb/IX or more platelet membrane glycoproteins; which bind to circulating platelet membrane [1-3]. Auto-antibody coated platelets induce Fc receptor mediated phagocytosis by mononuclear macrophages primarily in the spleen [2]. The resultant thrombocytopenia manifests as bleeding tendency, easy bruising (purpura), or extravasations of blood from capillaries into skin and mucous membrane (petechiae). Therefore thrombocytopenia and its sequelae are common to both ITP and acute leukemia in general.

An unexpected relationship between diseases was previously documented. In 1978; Ihara et al. [4] reported a case of AML in a 29 year old female in 10 years course of ITP with episodes of splenectomy and of safe delivery of a baby girl. Also reported was AML that strangely emerged from a diagnosed breast carcinoma patient within one month of diagnosis [5]. Also, an unusual case of AML masquerading as ITP was reported in this center [6]. A detailed literature search did not reveal any link in respect of existing pathogenesis between AML and ITP as well as any direct link between ALL and ITP except for a report of nine cases of ITP in children with ALL; three of them were acute ITP, and rest were chronic ITP [7]. Hence, the need for this case report which hereby suggests a possible link between ALL in remission and ITP by its clinical presentation and laboratory profile.

Case Presentation

The case is that of a 19 years old man, an undergraduate who was seen in the University College Hospital Ibadan in March 2012. He presented with a day history of total haematuria and gum bleed, prolonged bleeding from punctured sites and redness of both eyes. There was no previous history of bleeding diathesis. There was no family history of cancers.

He was diagnosed with adult polycystic kidney disease in India 2 years previously following severe systemic hypertension and has been on anti-hypertensive – Tabs Valsartan 160 mg daily and Tabs Carvedilol 25 mg bd. His mother had adult polycystic kidney disease post renal transplantation in India. He is the 2nd of three children in a monogamous family setting.

The physical examination at presentation revealed a young man who was well built, fully conscious and alert, not pale, afebrile, anicteric with extensive bilateral sub-conjunctival haemorrhages, petechiae haemorrhages on the lips, gum bleeds, a left lower cervical lymphadenopathy and no pedal edema.

The chest examination revealed no abnormalities. The Cardiovascular system revealed a pulse of 100 beats per minute, blood pressure was 160/120 mmHg with heart sounds I and II only. The abdomen was full and moves with respiration, moderate generalized tenderness and guarding, both kidneys were bimanually palpable but there was no palpably enlarged liver and spleen.

He was admitted and managed by the Haematology and Nephrology teams. Complete blood counts at presentation showed haematocrit of 0.38, white cell of $6.5 \times 10^9/L$, platelet count of $6.0 \times 10^9/L$, Neutrophils-61%, lymphocytes-29%, monocytes-8%, Eosinophils-1% and Basophils-1%. The peripheral blood film review showed red blood cells with moderate hypochromia and severe microcytosis (Figure 1). The white cells showed primitive intermediate sized lymphoblasts with high nucleo-cytoplasmic ratio and pale blue agranular cytoplasm. Some of these cells have 1-2 prominent nucleoli. These lymphoblasts constitute about 40% of all circulating white cells. There was also

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Received March 31, 2015; **Accepted** April 24, 2015; **Published** May 03, 2015

Citation: Olaniyi JA, Ogundeji PS, Ogbaro DD (2015) Immune Thrombocytopenic Purpura Following Acute Lymphoblastic Leukemia in Remission. J Leuk 3: 180. doi:10.4172/2329-6917.1000180

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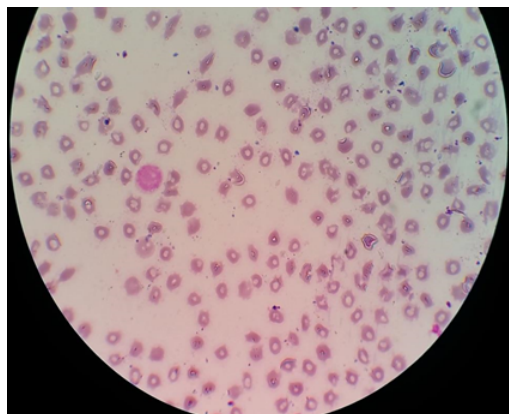


Figure 1: Initial peripheral blood photomicrograph showing severely hypochromic and microcytic red cells and a circulating lymphoblast with prominent nucleolus.

neutrophil left shift and toxic granulations. Platelets estimate was less than $10 \times 10^9/L$.

The bone marrow aspiration cytology showed intermediate to large sized lymphoblasts with high nucleo-cytoplasmic ratio (Figure 2). Myelopoiesis showed sequential maturation along the cell lines. Megakaryocytes were not seen. The lymphoblasts constituted 60% of bone marrow nucleated elements. A diagnosis of acute lymphoblastic leukemia (ALL) (L1-FAB) was therefore made. Other results of investigations normal electrolyte and urea but a uric acid 0.43 mmol/L, hyperuricaemia, Calcium- 2.15 mmol/L, and phosphate- 0.94 mmol/L. Liver function tests showed total bilirubin-41.7 $\mu\text{mol/L}$, direct bilirubin-8.3 $\mu\text{mol/L}$, total protein-72 g/L, albumin-44 g/L, AST-37 iu/l, ALT-21uI/L. Retroviral screening was non-reactive and hepatitis B surface antigen was negative. Coagulation profile showed Prothrombin time of 19 seconds, control 14 seconds, INR-1.5, APTT TEST -29 seconds, and control- 30 seconds. Abdominal ultrasound revealed an enlarged liver with a cranio-caudal span of 16.3 cm at MCL. It shows normal parenchymal echogenicity with no intrahepatic mass lesion or ductal dilatation seen. Both kidneys were enlarged with heterogeneous parenchymal echogenicity. They show multiple well defined, non-communicating anechoic oval shaped structure consistent with cyst. Some of the cysts show hyper echoic collections within them suggestive of intra-lesional haematoma. The central sinus is however well preserved. Other available investigations serum iron-32.1 $\mu\text{mol/l}$ (12.0-30.0), serum transferrin-1.7 g/l (1.6-3.2), % saturation 73.8% (20.0-55), serum ferritin 488.3 $\mu\text{g/l}$ (20-300).

The patient was resuscitated with red cell and platelet concentrate infusion and then commenced on pre-induction chemotherapy with intravenous Vincristine weekly and tablet prednisolone 20 mg tds (V+P) for 4 weeks. He had a significant response to the V+P therapy by normalization of platelets counts to $335 \times 10^9/L$.

He subsequently went to India where he was further evaluated and the diagnosis of ALL was sustained as evidenced by about 10% and 20% lymphoblasts in the peripheral blood and bone marrow respectively. A molecular study was in keeping with standard risk. He had Hyper CVAD (Cylophosphamide 1200 mg, Doxorubicin 100 mg, Vincristine 2 mg, Dexamethasone 40 mg daily $\times$ 4 days) and intra-theca (IT) 12.5 mg methotrexate in April 9, 2013. He also had IV Asparaginase 5000 IU in April 17, 2013. In May 2103 he had high dose ARA-C (2G alternate days for 3 days from 02/05/13), followed by high dose methotrexate (6

gm) on 23/5/2013. He was subsequently commenced on maintenance 6 Mercaptopurine and per oral methotrexate. He was then referred back to us for follow up.

At the second presentation in July 2013, his complete blood count showed haematocrit of 0.34 white blood cell count of $2.9 \times 10^9/L$ (neutrophil-46%, lymphocyte-50%, eosinophils-2% and monocyte-2%) and platelets count of $153 \times 10^9/L$. The peripheral blood film review still showed about 30% lymphoblasts in circulation. He was thus assessed not to be in remission. He was thereafter lost to follow up.

He presented for the third time in December 2013 for re-assessment and a repeat bone marrow examination showed a normo-cellular marrow with micro-normoblastic erythropoiesis, sequential maturation of the myeloid series and adequate Megakaryocyte with evidence of platelet budding (Figure 3). Also present were degenerating lymphoid cells constituting about 10% of the marrow elements. The assessment of ALL in partial remission was made. He continued with the maintenance therapy with oral methotrexate and 6 Mercaptopurine but again he was lost to follow up.

He represented in January 2015, while still on his maintenance therapy, on account of a repeat total haematuria and sub-conjunctival haemorrhage. The peripheral blood film review showed marked thrombocytopenia without evidence of circulating lymphoblast. A bone marrow aspiration cytology at this time revealed normo-cellular marrow with micro-normoblastic erythropoiesis, sequential maturation of the myeloid series. Megakaryocytopenia was increased

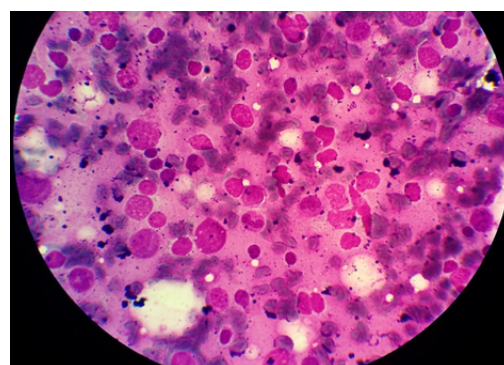


Figure 2: Initial bone marrow film showing numerous lymphoblasts and absence megakaryocytes.

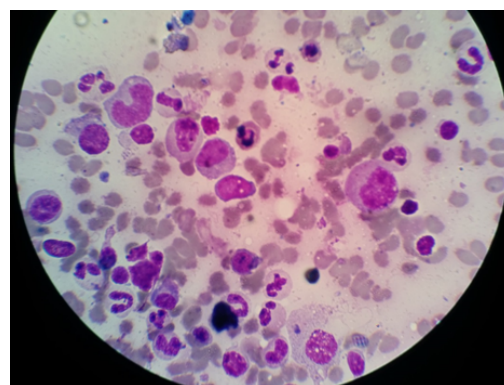


Figure 3: Second repeat bone marrow photomicrograph showing a normal marrow while on maintenance chemotherapy.

with 5-7 megakaryocytes seen per $\times 10$ objective and they were of low ploidy, cytoplasmic basophilia and have smooth non-budding nuclei (Figure 5). The assessment of Immune Thrombocytopenic purpura was made. He was commenced on steroid therapy with oral prednisolone 20 mg tds which he responded to with normalization of platelets counts and resolution of bleeding. The patient has remained in remission after being treated with prednisolone for a total period of three months but would require regular follow up to monitor progress.

Discussion

While acute leukemia is known to be an aggressive disease that usually presents with features of bone marrow failure, presence of excess of blasts in the bone marrow, spillage of blasts into the peripheral circulation and evidence of multiple tissue infiltration [8-12]; ALL is a malignant disorder of lymphopoietic stem cells that originates in the lymphoid precursor of marrow, thymus and lymph nodes. Untreated ALL is usually fatal within 6 months, but with the best therapy 70-80% of children and 20- 30% of adults survive beyond 5 years [13]. Acute leukemia in remission followed by ITP was not found in the course of our literature even though, found documented are many ITP associated disorders [14,15] involving lymphocyte abnormalities like large granular lymphocyte syndrome, lymphoproliferative disorders like Chronic Lymphocytic Leukemia (CLL) and lymphomas, others include autoimmune lymphoproliferative disorders, autoimmune haemolytic anaemias, Systemic Lupus Erythematosus (SLE) and antiphospholipid syndrome; direct link of ALL with ITP is yet to be reported in literature. The closest reported was AML masquerading as ITP [6].

The patient, when diagnosed of ALL mainly by the thrombocytopenic bleeding, presence of solitary cervical lymphadenopathy, finding of lymphoblast on blood smears and bone marrow smears, was not acutely ill, not anaemic and there was no neutropaenia.

Immunophenotyping and molecular studies would have helped in characterizing the disease but facilities for such studies were not readily available. However, further evaluation of this patient in India still confirmed ALL for which Induction chemotherapy, followed by consolidated chemotherapy for ALL were instituted. He was back to Nigeria while on Maintenance chemotherapy. All these reinforced the diagnosis of ALL.

This patient remained well and was fit enough to cope with his undergraduate studies over the three years of diagnosis except for the notable two episodes of bleeding. The recent re-presentation with total haematuria, florid petechiae haemorrhage, with a platelet count of

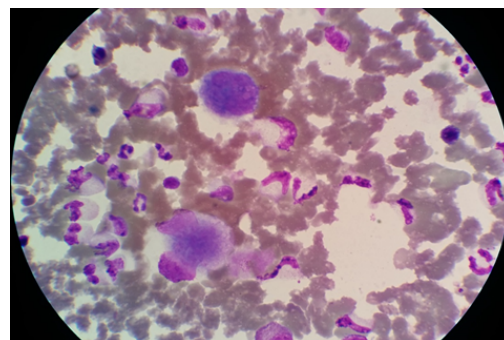


Figure 5: Bone marrow photomicrograph showing Megakaryocytes with low ploidy, cytoplasmic basophilia and smooth non-budding nuclei.

10,000/mm³, blood and marrow smears being devoid of lymphoblasts created a puzzle. However the finding of numerous, smooth non-budding megakaryocytes of up to six at low power and about two at high power objective suggested ITP (Figure 4).

Therefore the substantive question to answer at this point is what is the link between ALL and ITP? A prospective study of ITP in 245 adults, carried out in 2003 [16] showed an overall incidence 1.6/100,000/yr., median age 56, F:M 1.2:1, 12% presented with bleeding, 28% asymptomatic, 18% needed no treatment, only 12% needed splenectomy, 63% in remission (plts>100 $\times 10^9$ /L) at end of follow up period (6-78 months, median 60), 87% had at least partial remission (plts>30 $\times 10^9$ /L) and freedom from symptoms, 1.6% died from complications of disease or its treatment. This study did not report any association between acute leukemia and ITP.

In conclusion this case report strongly suggests that a possible pathogenetic link exists between acute leukemia and ITP which requires detail investigation.

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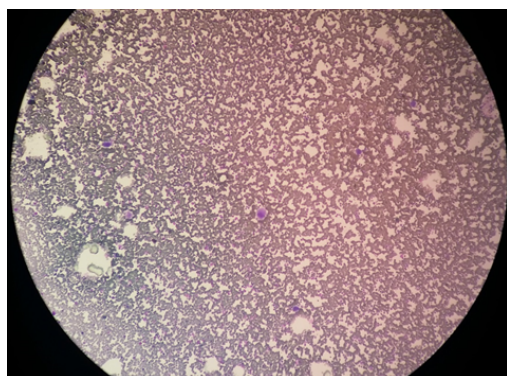


Figure 4: Bone marrow photomicrograph taken in February 2015 showing 6 megakaryocytes. X10 lens objective.

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