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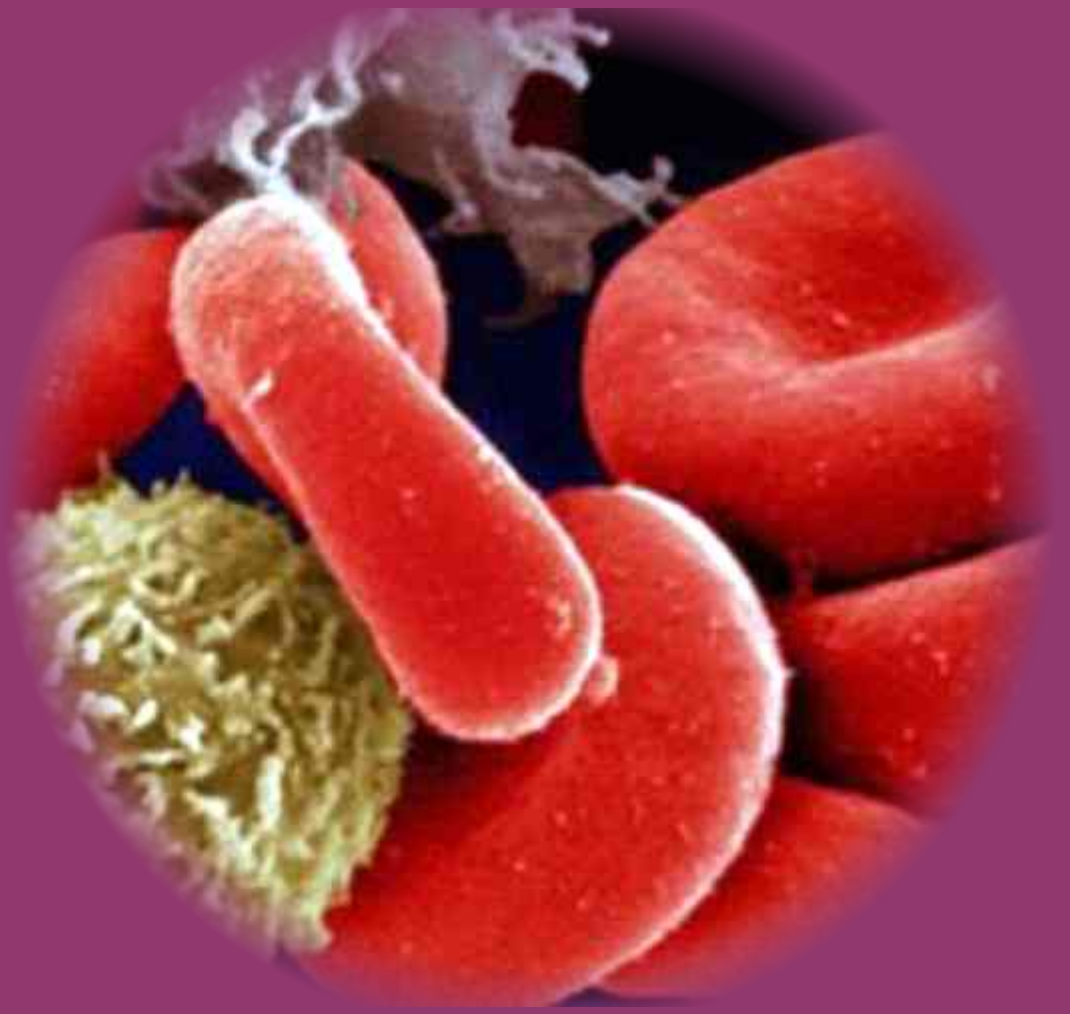

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Challenges of Management: Necrotizing Fasciitis Complicating Acute Lymphoblastic Leukaemia in a Resource Limited Setting

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SUMMARY

A 17 year male student presented with features of acute lymphoblastic leukaemia (L2 morphology) with severe thrombocytopenia, complicated by anaemic heart failure. He had limited resources being fatherless and had no access to the National Health Insurance Scheme (NHIS). While on admission he developed necrotizing fasciitis (NF) Type II. The cultured microorganism was *Staphylococcus aureus*. Treatment was irregular and his condition was complicated by Gram negative septicaemia. The patient could not afford treatment and died of shock. Necrotizing fasciitis is being reported here for the first time in a patient with leukaemia in Nigeria. The risk factors for NF, the challenges of managing a patient with limited resources and the need for a multidisciplinary care approach have been discussed.

Keywords: necrotizing fasciitis, acute lymphoblastic leukaemia, immunosuppression, limited resource setting

INTRODUCTION

Necrotizing fasciitis is a rare condition with high mortality. It has been reported to be associated with immunosuppression, malignancy, hyperglycaemia, end-stage renal failure, pulmonary diseases, injection drug abuse, peripheral vascular disease, obesity and burns. Infection in Necrotizing fasciitis (NF) is expensive to treat, especially when the underlying disease is a malignancy as seen in this case. Unfortunately, this patient had limited resources that contributed to the mortality which is normally between 80 to 100%.

Case presentation

A 17 year old male student who presented with progressive left sided abdominal swelling of fourteen (14) days duration, generalized body weakness of one week duration and bilateral leg swelling of five (5) days duration. The abdominal swelling was associated with dull abdominal pain, easy satiety, weight loss and high grade intermittent fever. He had mild exertional dyspnoea, orthopnea and progressive bilateral leg swelling. He was treated at home with antimalarial and antibiotics (oral Ciprofloxacin) and when symptoms did not abate, he was taken to the hospital for expert management. He is not known to have hypertension, diabetes mellitus, asthma or sickle cell disease and he is not on any routine medications. He had no previous history of surgery or blood transfusion. He is the second child in a family of four in a monogamous setting, but his father died five years ago from an unknown cause. He could not afford national health insurance (NHIS).

Findings on physical examination

Vital signs: Temperature - 38.4 ^{0}C; pulse rate - 130 b/m; blood pressure - 120/80 mmHg; respiratory rate - 36 c/min. He weighed 60kg and was173cm tall (BMI-20.0 kg/m^2). He was acutely ill-looking, febrile, dyspnoeic, markedly

pale, with petechial haemorrhages on the chest and forearms bilaterally, generalized lymph node (LN) enlargement (largest measured 3cm x 2cm, firm, rubbery, mobile and non-tender) and bilateral pitting pedal oedema up to just below the knees. Chest examination revealed bilateral fine basal crepitations. Cardiovascular signs included tachycardia, raised jugular venous pressure, a displaced apex beat at 5th left intercostal space (5LICS) slightly outside the mid clavicular line (MCL). There was gallop rhythm. There was splenomegaly 12 cm and hepatomegaly 8 cm below the left and right costal margins respectively.

PERIPHERAL BLOOD FILM (X 400)

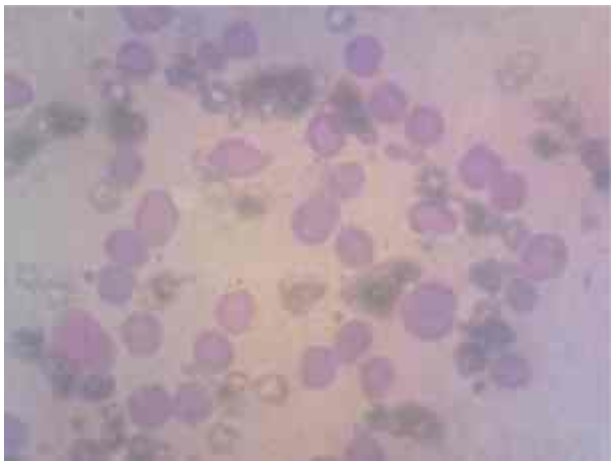

Figure 1: Peripheral blood film showing leukocytosis, lymphoblasts of varying sizes, microcytosis, hypochromia and thrombocytopenia in a patient with acute lymphoblastic leukaemia (L2)

BONE MARROW ASPIRATE (X 100)

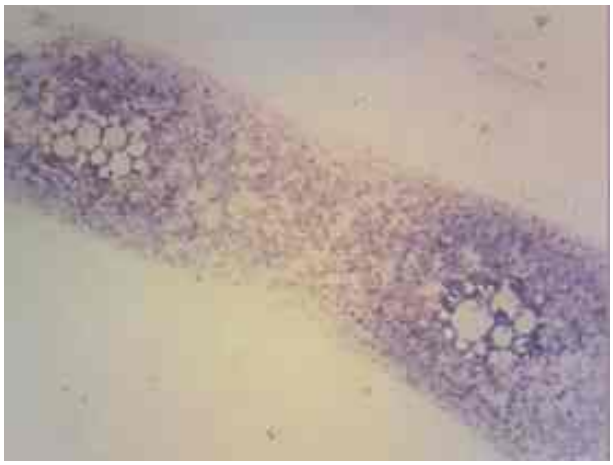

Figure 2: Hypocellular fragments from the bone marrow of a patient with acute lymphoblastic leukaemia (L2)

Investigations

Full blood count and peripheral film (Figure 1) showed marked leukocytosis (134.0 x 10^9/L) consisting predominantly of heterogenous lymphoblasts (96%), severe microcytic hypochromic anaemia (PCV = 8%; MCV = 78fl; MCH = 27 pg; MCHC = 34mg/dl; RDW = 14.7%) and severe thrombocytopenia (3.0 x 10^9/L). The bone marrow aspiration (Figure 2) showed hypocellular fragments and predominantly heterogenous lymphoblasts constituting more than 90% of the nucleated bone marrow cells. Erythropoiesis was depressed and micronormblastic, granulopoeisis was the direct Coombs test was negative, ESR was 130 mm/hr, reticulocyte count was 3.4% (corrected count was 0.7%), malaria parasite was absent, pre-treatment FBG was 5.1mmol/l. The blood chemistry is as shown in Table 2. The abnormalities that persisted after rehydration were hypoalbuminaemia, elevated SGPT and SGOT. Cytogenetic analysis revealed normal karyotyping and BCR-ABL was negative, immunophenotyping could not be done due to financial constraint.

A diagnosis of acute lymphoblastic leukaemia (L2 morphology) with severe thrombocytopenia, complicated by anaemic heart failure was made.

Treatment:

The patient received a total of seven units depressed with sequential maturation, megakaryopoeisis was also depressed, but with normal morphology, plasma cells were not increased, foreign cells were not seen of pack cells, two units of fresh unbanked whole blood and two units of platelet concentrates during admission (Table 1).

He was commenced on parenteral antibiotics (Ciprofloxacin and Metronidazole) and received low salt and egg white fortified diet because of the hypoalbuminaemia and low BMI. He was commenced on allopurinol, hydration and pre-induction Vincristine (1.4mg/m^2) and Prednisolone (60mg/m^2; VP) regimen for one week.

Table 1: Full blood counts from admission to day 55

Day from Admission	PCV (%)	WBC (x 10^9)	NEUTROPHILS (%) (ANC x 10^9)	LYMPOCYTES (%)	LYMPHOBLAST (%)	PLATELETS (x 10^9)
0	8	134.0	01	03	96	15.0
Two units of fresh unbanked packed red cells and two units of platelets were transfused						
4	20	3.5	25 (0.9)	30	45	24.0
One unit of fresh unbanked packed red cells was transfused						
6	21	1.2	30 (0.36)	40	30	28.0
One unit each of packed red cells was given on 3/3/17 and 4/3/17 respectively.						
10	23	0.8	62 (0.5)	32	6	16.0
One unit of packed red cells was transfused						
20	23	4.6	75.5 (3.47)	21.2	-	65.0
One unit of packed red cells was transfused.						
38	30	6.8	58 (3.88)	42	-	175.0
55	36	10.1	77 (7.7)	20.7	-	467.0

Table 2: Blood chemistry results and prothombin time/INR

Day from admission	Na+ (mmol /L)	K + (mmol /L)	Corrected Calcium (mmol/L)	Urea (mmol /L)	Cr (µmol /L)	Alb (g/L)	Uric acid (mmol/L)	SGOT (i.u/L)	SGPT (i.u/L	ALP (i.u/L)
0	133	3.4	2.3	6.3↑	76	33↓	0.24	40↑	37↑	178
4	132	5.9	2.16	3.4	63	30↓	0.6↑	48↑	45↑	493↑
8	129	4.7	2.24	3.2	60	30↓	0.33	-	-	335↑
26	127	3.4	2.5	3.8	40	28↓	0.14	68↑	60↑	277↑
53	143	4.1	-	3.7	43	31↓	0.35	12	10	273↑
	PT (sec)	**INR**								
17	15	1.1								
28	15.5	1.2								

On the sixth day of pre-induction VP, he developed steroid-induced hyperglycaemia with a FBG level of 15.7 mmol/l (Pre-treatment FBG was 5.1mmol/L) and fever (Day 5 ANC was 895 x 10^9/L; Table 1). He was reviewed by the endocrinologist who placed him on soluble insulin (Apidra®) 8 IU 8hrly, however, he could not commence treatment because of financial constraint until 7/3/2017 (Day 11) when the endocrinologist donated some soluble insulin. Table 3 shows the changes in the FBG and RBG values. On completion of pre-induction VP, the blast count was 30%, ANC was 360 cells x 10^9/L and platelet count was 28,000 x 10^9/L. The patient no longer had LN enlargement, but he was unable to commence definitive chemotherapy with Daunorubicin, Cyclophosphamide and Prednisolone regimen

because of the severe neutropenia and thrombocytopenia, which necessitated the continuation of pre-induction, VP. He developed swelling of the right upper limb on the sixteen (16) days post-admission which was tender, with differential warmth, hyperaemic with bullae of various sizes on the dorsum of the hand and medial surface of the arm, there was no tissue crepitus. Figure 3 shows the skin lesions on Days twenty (20) and thirty-five (35) respectively. The lesions extended to the right lower limb and an impression of cellulitis secondary to immunosuppression was made by the Plastic Surgeons who recommended that the wound be elevated and dressed daily with Povidone iodine. The Medical Microbiologists reviewed later and made a diagnosis of necrotizing fasciitis with about 7% of full skin thickness loss. A wound biopsy was requested, but could not be obtained do to financial constraint. The culture of the aspirate from the bullae yielded Methicillin resistant

Staphylococcus aureus which was sensitive only to Vancomycin. He was subsequently commenced on I.V. Vancomycin 500mg 8hrly. He received irregular average daily doses of 500mg or 1g due to financial constraint and his temperature returned to normal. Escharectomy was done several times by the Plastic Surgeons and the wound was

Table 3: Blood glucose levels from day 1 to 54

DAY FROM ADMISSION	FBG (mmol/L)	RBG (mmol/L)
1	5.1	19.3
5	15.7-SC Glargine 8i.u nocte	
9	9.5	17.1
10	11.5	14.5
11		7.5
14	7.4	
16	4.8	
18	8.0- SC Glargine↑ to 10i.u nocte and SC Apidra 10i.u 8hrly	
35	4.6	
42	5.2	10.7
54	4.1	

Table 4: Full blood counts from day 60 to 76

Day from admission	PCV (%)	WBC (x 10^9)	Neutrophils (%)	Stab forms (%)	Lymphocytes (%)	Myelocytes (%)	Metamyelocytes (%)	Lymphoblasts (%)	Platelets (x 10^9)	ANC (x 10^9)
60	41	40.8	35	21	14	10	0	14	231.0	26.9
63	35	44.2	10	10	06	02	04	68	60.0	11.5
Commenced on induction regimen I.V. Daunorubicin (Day 1-3), Tab Prednisolone 40mg/m2, (Day 1-28), I.V. Vincristine 1.4mg/m2(Days 1,8,15,22)										
66	33	3.15	48	17	32	0	0	02	82.0	2.05
69	31	2.8	52	0	35	0	0	0	79.0	1.46
73	29	3.4	56	04	40	0	0	0	82.0	1.9
76	27	1.2	50	0	50	0	0	0	106.0	0.6

subsequently dressed daily with honey. On Day 60 it was noticed that the blast count in the peripheral blood had increased to 14%. The relatives could not procure the prescribed chemotherapy until three days later when the blasts increased to 68%. Chemotherapy was made available for three days only and subsequently the blasts reduced to 2% and then to zero percent (Table 4). On Day 67 the high grade fever returned and a blood culture revealed Gram negative bacilli that yielded multidrug-resistant Klebsiella specie sensitive to only Imipenem. The patient was unable to procure Imipenem and the chemotherapeutic agents needed to complete his first induction due to financial constraint. He went into shock and died on Day 78.

DISCUSSION

Necrotizing fasciitis (NF) is a rare but often fatal bacterial infection of the skin, subcutaneous tissue and fascia with mortality rates in adults ranging from 80% to 100%.[1, 2] This condition has been in existence for over a century as haemolytic gangrene, acute streptococcal gangrene, gangrenous erysipelas, necrotizing erysipelas, suppurative fasciitis and hospital gangrene, but the term necrotizing fasciitis was first proposed in 1952 by Wilson. [3, 4] Necrotizing fasciitis is classified into four based on the causative organism(s): Type I - polymicrobial, Type II - monomicrobial, Type III - gram-negative, or gas gangrene and Type IV - fungal.[5]

Necrotizing fasciitis is more common in middle-aged adults, without sex, race, or geographic predilection. [6] The incidence of necrotizing fasciitis is very rare in acute leukaemias. In an extensive review of the literature, Lorenzen *et al* (2011) reported a total of 19 incidences of NF in leukaemias, with nine in acute myeloblastic leukaemia, four in acute non-lymphatic leukaemia, five in acute lymphoblastic leukaemia, and one in chronic lymphocytic leukaemia.[7]

The case reported here is Type II NF being due to a monomicrobial isolate of Methicillin resistant *Staphylococcus aureus*. The risk factors in this patient included the underlying acute leuakaemia, immunosuppression from the leukaemia and steroid therapy and steroid-induced hyperglycaemia. Other predisposing factors that were not present in this patient are end-stage renal failure, pulmonary disease, injection drug abuse, peripheral vascular disease, obesity and burns. In some cases, the predisposing factor may be unknown. [8] Necrotising fasciitis has been reported in some conditions other than leukaemia in adults and children in Nigeria, [8] but to the best of our knowledge, this is the first report of NF in Nigeria in any patient with leukaemia.

The site of presentation of NF in this patient involved the right upper and lower limbs, this is in agreement with earlier reports that in adults, the lower extremities are more frequently affected, followed by the trunk and head.[9] The diagnosis in this case was both clinical and laboratory. The clinical features in this patient fit into what has been described earlier as the nature of NF, that is, a “flesh eating bacteria syndrome”.[10] Histology, CT scan, and MRI had been advocated for early diagnosis of NF, but none of these investigations could be done in this patient because of financial constraint, however, MRI, has been reported to be the best tool in early diagnosis. The wound culture yielded Methicillin resistant *Staphylococcus aureus*, this is in keeping with one of the usual causative organisms. [11] The patient was treated with intravenous Vancomycin to which he responded despite irregular administration due to financial constraint. [2] Lack of funds is not unusual in most patients with cancer in Nigeria as reported by Durosinmi *et al* (1993) in the era of the structural adjustment programme. [12] The NHIS was introduced about 12 years ago to assist Nigerians access health care, but coverage is poor as it does not provide for many anti-cancer agents. According to Obadan *et al* (2016), only 7.9 million out of 186 million Nigerian population (4.2%) have registered on NHIS.[13]

Figure 3: Necrotizing fasciitis: (A) At Day 20 involving right upper limb showing bullae and extensive necrosis of the skin. (B) At Day 35 involving both right upper and lower limb following minimal escarectomy revealing involvement of skin, subcutaneous tissue sparing the underlying muscles.

Early diagnosis and surgical debridement which were ensured in this patient should have contributed to improving his chances of recovery and survival as indicated by Legbo *et al* in 2005, but for the underlining ALL and the associated complications.[14] It is not unusual to see adult patients with good prognostic type of ALL respond quickly to VP. Hess *et al* (1982) reported that approximately two-thirds of adults with ALL will achieve complete remission (CR) with the use of Vincristine and Prednisolone alone. The median duration of CR was less than one year and the median survival was approximately two years.–[15] This patient had an early but short-lived response to VP given irregular due to financial constraint. If he had NHIS coverage, his survival could probably still be in doubt because, although Imipenem needed for the secondary infection is available under NHIS, it may not be available within the hospital pharmacy and it is expensive. Limited resources made it difficult to manage this patient and just may be he could have survived if he had NHIS cover.

CONCLUSION

We have presented a rare case of NF in a patient with acute lymphoblastic leukaemia who had immunosuppression as the primary risk factor in addition to the complications of treatment (steroid-induced hyperglycemia). The challenges of managing such a patient who did not survive due to limited resources have been highlighted. It is worthy of note that a high index of suspicion for NF and a multidisciplinary approach to its management, as employed in this case, may enhance survival of such patients even when resources are available.

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Conflict of Interest:
No conflict of interest was declared by the authors.

Contribution of Authors:
The first five authors contributed to the writing of this manuscript and others contributed to the review and all contributed to the management of this patient.

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