A case of a periosteal reaction in a patient with paroxysmal nocturnal haemoglobinuria newly diagnosed with acute myeloid leukaemia: A South African perspective

Garrick E. Laudin[*,1], **Peter F. Levay**[*] **and Gugulethu Ndhlebe**[*]

[*]University of Pretoria, Department of Internal medicine, Kalafong Provincial Tertiary Hospital, 1 Klipspringer street, Atteridgeville, Pretoria 0008, South Africa.

ABSTRACT Paroxysmal nocturnal haemoglobinuria is an orphan disease and is a deficiency in more than one GPI-linked protein on red cells which makes them vulnerable to complement-mediated lysis. The availability of treatment for PNH in the form of eculizumab is currently not available in resource-poor countries such as South Africa.

The rare clinical manifestation of a periosteal bone reaction and upper limb swelling in a 28-year-old male patient with an established diagnosis of PNH prompted exclusion of infectious and thrombotic causes for the presumed periostitis and swollen limb. Further examinations of haematological parameters revealed the presence of blasts with flow cytometry confirming acute myeloid leukaemia.

KEYWORDS Leukaemia, Acute Myeloid Leukaemia, Paroxysmal Nocturnal Haemoglobinuria, periosteal reaction, Rheumatology

CASE REPORT

Mr GSM, a 28-year-old South African male, was diagnosed with paroxysmal nocturnal haemoglobinuria on immunophenotyping on peripheral blood which demonstrated a deficiency in more than one GPI-linked protein, on more than one cell lineage.

He had no other co-morbid conditions, was HIV negative and current hepatitis studies were negative for hepatitis A, B and C.

Previous admissions to our facility were for treatment of suspected upper limb osteomyelitis for which our patient received a month of intravenous antibiotics in the form of cloxacillin and vancomycin. He had been previously admitted for transfusion of blood products.

DOI:10.5455/IJMRCR.paroxysmal-nocturnal-haemoglobinuria-hematuria
First Received: February 18, 2020
Accepted: March 03, 2020
Manuscript Associate Editor: Ivan Inkov (BG)

[1]University of Pretoria, Department of Internal medicine, Kalafong Provincial Tertiary Hospital, 1 Klipspringer street, Atteridgeville, Pretoria 0008;
Email:Garrick.laudin@gmail.com

Our patient presented on this admission with a history of bilateral upper limb swelling as well as left leg swelling. He reported no history of myalgia or arthralgias. The swelling of the left leg subsequently resolved. Skin swabs of lesions of the upper limbs were negative for methicillin-resistant Staphylococcus aureus (MRSA) with blood cultures also demonstrating no growth of Staphylococcus aureus.

Owing to the soft tissue swelling of the upper limbs, there was a concern for both an underlying infective process or a thrombotic complication of PNH. X-rays of the upper limbs revealed the appearance of a periosteal reaction of the right upper limb ulna with X-rays of the left footnoting a periosteal reaction of the fifth metatarsal (see figure below). Upper limb dopplers demonstrated patency in the venous system. Bone marrow Tc-99m-HMPAO leucocyte scintigraphy failed to show any underlying infective process in the region of the upper limbs.

Physical examination revealed the presence of a palpable spleen. Abdominal ultrasonography demonstrated hepatosplenomegaly with the splenic size noted as 121 by 66 mm. The splenic parenchyma was reported as coarse, but no splenic masses were documented. The liver did not appear to be cirrhotic, but the texture was reported as "coarse". Both the hepatic portal vein and splenic vein were patent on ultrasonography.

A complete blood count with a peripheral smear initially

made a comment of blasts noted with a suggestion for a bone marrow biopsy. Bone marrow trephine revealed a hypercellular marrow infiltrated with blasts with immunophenotyping revealing CD34 population of cells.

Flow cytometry revealed acute myeloid leukaemia with a monocytic component. Cytogenetics revealed 95% of the cells had an extra copy of the RUNX1 gene while the remainder of the FISH results were negative (see results in table one).

Our patient was transfused with packed red blood cells and platelets and was transferred to an oncology centre within our University for ongoing care.

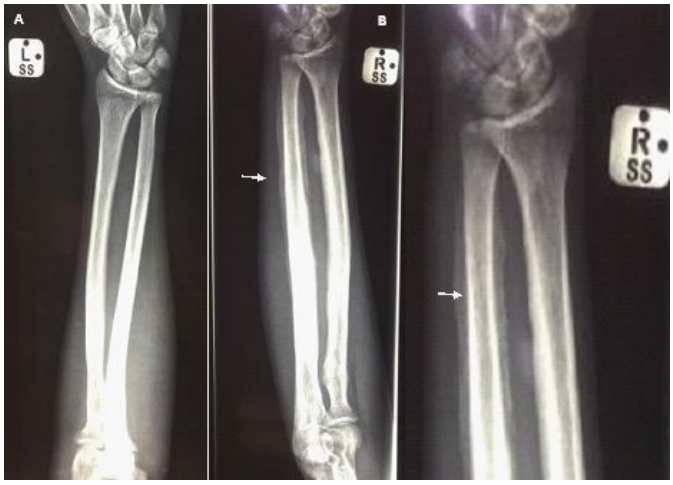

Figure 1: (A) Left radius and ulna (no periosteal reaction), (B) AP and lateral X-ray of the right radius and ulna with a multilayer periosteal reaction (white arrow), (C) Magnified image of the periosteal reaction of the distal ulna (image reporting courtesy of Dr Nakasholo – Department of Radiology, Kalafong Provincial Tertiary Hospital).

DISCUSSION

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haematological disorder, with PNH incidence is estimated at 1–1.5 cases per million individuals worldwide, the basic pathophysiology of which being the result of a deficiency in GPI-anchored red blood cell proteins CD55 and CD59[2]. The absence of the GPI-anchored proteins on the red cells stems from somatic mutations in the X-linked PIGA gene in one or more clones of multipotent haematopoietic stem cells[2]. This loss of function mutation may also result in a deficiency in GPI-anchored proteins in all haematopoietic cell lineages[2]. Haemolysis in PNH is because of complement-mediated red cell haemolysis due to a deficiency of complement inhibitors CD55 and CD59 on red cells[2]. The presence of pancytopenia in our patient was likely the result of the involvement of multiple cell lineages with a deficiency in GPI-anchored proteins.

Various types of acute leukaemia have been reported in PNH, including myeloblastic, monocytic, myelomonocytic" and megakaryoblastic. In some reports in the literature, the development of myelofibrosis in patients with PNH has been complicated by the development of acute myeloblastic leukemia[10]. It is unclear if the development of acute leukaemia in PNH arise from the abnormal PNH clone or another clone within the damaged marrow[12].

Myelodysplasia has been considered as one of the clinical sequelae of PNH, with the defects in myeloid stem cell function

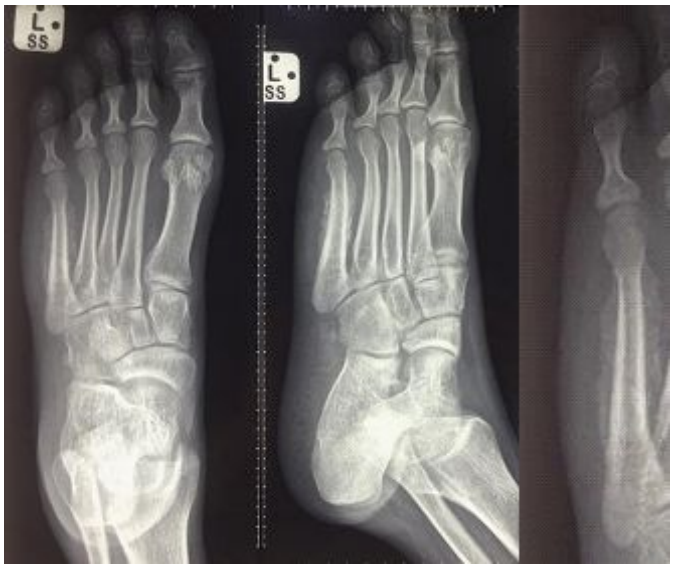

Figure 2: X-rays of the left foot, demonstrating a periosteal reaction of the fifth metatarsal. A magnified image of the fifth metatarsal is present alongside

implicated in the subsequent development of acute myeloblastic leukemia[11].

Reports of a periosteal reaction occurring during acute leukaemia are rare and are mostly reported in the paediatric population. A periosteal reaction reported in paediatric patients may be heralded by the presence of significant limb swelling[3].

Early reports of bone changes in leukaemia, both lymphocytic and myeloid leukaemia, the bones in general were found to be either osteoporotic or osteosclerotic, with or without periostitis[7].

The rheumatological manifestations of acute leukaemia may present with bone pain, bone tenderness as well as a polyarthritis or arthralgia and in some instances may be the presenting complaint prior to the diagnosis of the haematological malignancy. The involvement of the periosteum of the bone may be due to haemorrhage with synovial involvement of the bone due to direct infiltration by leukemic cells[4]. In order to prove the latter in this patient, a bone biopsy would have been ideal.

PNH is associated with chronic intravascular haemolysis with resultant hemosiderinuria and hemoglobinuria[8]. Patients with PNH often require repeated transfusions of packed red blood cells, and iron overload may develop with the transfusion of more than 15 to 20 units of packed red cells[9]. Patients who receive chronic transfusions of blood products are generally monitored with serum ferritin levels, with ferritin levels exceeding 1000 – 1500 ng/mL prompting imaging to monitor for liver or cardiac involvement[9]. Iron chelation therapy would, therefore, be advised in this patient.

While the presence of splenomegaly in PNH may represent thrombosis due to PNH complicated by Budd Chiari syndrome, the other causes for the presence of splenomegaly may also be due to the co-existence of a hemoglobinopathy[13,14]. Splenomegaly is reported in less than ten percent of cases of PNH with most cases resulting from venous thrombosis arising from sites like the portal vein or splenic vein15. It is also another postulate that involvement of leukemic cells in our patient may have been a cause for the splenomegaly with a proposal that this patient's pancytopenia being multifactorial and possibly due to

Table 1 Laboratory and cytogenetics results.

Laboratory parameter	Value	Laboratory Normal Value
Full blood count		
White cell count (x10^9/L)	3.10	3.92 – 10.40
Haemoglobin (g/dL)	5.1 **(L)**	13.4 – 17.5
Hematocrit (L/L)	0.157 **(L)**	0.390 – 0.510
Mean Cell Volume (fL)	85.3	83.1 – 101.6
Mean Cell Hemoglobin (pg)	27.7 **(L)**	27.8 – 34.8
Red cell distribution width (%)	15.2	12.1-16..3
Platelet count (x10^9/L)	3 **(L)**	171 - 388
Differential Count	**% (absolute)**	**Absolute x 10^9**
White cell count	3.10 x 10^9 **(L)**	3.92 – 10.40
Neutrophils	31% (0.96)	1.6 – 6.98
Lymphocytes	41 (1.27)	1.4 – 4.2
Monocytes	24 (H) with absolute	0.3-0.8
Blasts	0.74 (N)	
	4 (0.12)	
Inflammatory markers		
C-Reactive Protein (mg/L)	65 **(H)**	<10
Urea and Creatinine	Normal	
Iron Studies		
Iron (umol/L)	35.9 **(H)** 1.50 **(L)**	11.6 – 31.1
Transferrin (g/L)	95 **(H)**	1.74 – 3.64
% Transferrin saturation (%)	11526 **(H)**	20 – 50
Ferritin (ug/L)		22 – 275
Cytogenetics		
- deletion of 5q31 (EGR1) monosomy of	Negative	
- chromosome 5 deletion of the 7q31	Negative	
- region monosomy of chromosome 7	Negative	
- deletion of the TP53 gene	Negative	
- rearrangement of the KMT2A	Negative	
- (MLL) gene	Negative	
- translocation t(8;21)(q22;q22)	Negative	
- RUNX1/RUNX1T1 fusion gene	Negative	
- translocation t(15;17)(q24;q21)	Negative	
- PML/RARA fusion gene	Negative	

hypersplenism.

The complexity of this case is not only underpinned by the diagnosis of paroxysmal nocturnal haemoglobinuria but is also complicated by acute myeloid leukaemia with possible transfusional hemosiderosis. Our patient's medical management was subsequently continued by our oncology service, and indeed all these disease complexities will need to be addressed with possible further imaging of both the liver and heart prior to the commencement of chemotherapy.

ABBREVIATIONS

- Acute Myeloid Leukaemia (AML),
- Fluorescent In-Situ Hybridisation (FISH),
- Glycosylphosphatidylinositol (GPI),
- methicillin-resistant Staphylococcus aureus (MRSA),
- Paroxysmal Nocturnal Haemoglobinuria (PNH),
- Technetium exametazime (Tc-99mHMPAO)

ACKNOWLEDGEMENTS

University of Pretoria Department of Radiology (Dr Nakasholo), University of Pretoria Department of Nuclear Medicine (Dr Khanyisile Hlongwa & Dr Neo Mokoro), University of Pretoria Department of Hametaology Pathology (Dr JG Nel), National Health Laboratory Service (Dr P. Willem – Dept Haem, Head Somatic Cell Genetics Unit).

DISCLOSURE STATEMENTS

There were no financial support or relationships between the authors and any organization or professional bodies that could pose any conflict of interests.

COMPETING INTERESTS

Written informed consent has been obtained from the patient for publication of this case report and any accompanying images.

REFERENCES

1. Harris JW, Koscick R, Lazarus HM, Eshleman JR, Medof ME. Leukemia Arising out of Paroxysmal Nocturnal Hemoglobinuria. Leukemia and Lymphoma .1999; 32(5-6):. https://www.ncbi.nlm.nih.gov/pubmed/10048414 (accessed 31 March 2019).

2. Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. Nature Reviews Dis-

ease Primers .2017; 3(): . https://www.nature.com/articles/nrdp201728 (accessed 31 March 2019).

3. Ueda T , Ito Y , Maeda M, Fukunaga Y. Massive periosteal reaction a presenting feature of acute megakaryocytic leukemia Pediatrics International .2007; 49(6): . https://www.ncbi.nlm.nih.gov/pubmed/18045316 (accessed 05 April 2019).

4. Shah AA, Cappelli L. 2018. Malignancy and rheumatic disorders. UpToDate. Available: https://www-uptodate-com.uplib.idm.oclc.org/contents/malignancy-andrheumaticdisorders?sectionName=Leukemia&search=Clinical%20manifestations,%20pathologic%20features,%20and%20diagnosis%20of%20acute%20myeloid%20leukemia&topicRef=4510&anchor=H19&source=see_link#H19 (accessed 05 April 2019)

5. Kharazmi M, Carlson K, Björnstad L, Petersson A, Warfvinge G. Mandibular osteomyelitis associated with paroxysmal nocturnal hemoglobinuria. International Journal of Oral and Maxillofacial Surgery .2011; 40(12): 1441–1444. https://www.ijoms.com/article/S0901-5027(11)00253-0/fulltext (accessed 05 April 2019).

6. Gura H, Korena V, Ehrenfelda M, Ben-Bassatc I, Sidi Y. Rheumatic Manifestations Preceding Adult Acute Leukemia: Characteristics and Implication in Course and Prognosis. Acta Haematol .1999; 101(1): . https://www.karger.com/Article/Abstract/40913 (accessed 05 April).

7. Craver LF, Copeland MM. Changes of the bones in leukemia. Archives of Surgery 1935; 30(4): 639-646. https://jamanetwork.com/journals/jamasurgery/articleabstract/542226 (accessed 07 April 2019).

8. Neme-Yunes Y, Guerrero-Sánchez E, Pérez-Zepeda MU , López-Karpovitch X . Iron overload: an overlooked complication in classic paroxysmal nocturnal hemoglobinuria..Revista de Hematología. 2016; 17(4): . http://www.medigraphic.com/pdfs/hematologia/re-2016/re164b.pdf (accessed 08 April 2019).

9. Schrier SL, Bacon BR, Kwiatkowski JL. 2018. Approach to the patient with suspected iron overload. UpToDate. Available: https://www-uptodatecom.uplib.idm.oclc.org/contents/approach-to-the-patient-with-suspected-ironoverload?search=iron%20overload%20hemosiderosis&topicRef=7167&source=see_link (accessed 08 April 2019).

10. Nakahata J, Takahashi M, Fuse I, Nakamori I, Nomoto N, Saitoh H. Paroxysmal Nocturnal Hemoglobinuria with Myelofibrosis: Progression to Acute Myeloblastic Leukemia. Leukemia and Lymphoma. 1993; 12(): . https://www.ncbi.nlm.nih.gov/pubmed/7512853 (accessed 08 April 2019).

11. Krause J. Paroxysmal Nocturnal Hemoglobinuria and Acute Non - Lymphocytic Leukemia: A Report of Three Cases Exhibiting Different Cytologic Types. Cancer. 1983; 51(): . https://onlinelibrary.wiley.com/doi/pdf/10.1002/10970142(19830601)51:11%3C2078::AID-CNCR2820511121%3E3.0.CO;2-0 (accessed 08 April 2019).

12. Devine DV, Gluck WL, Rosse WF, Weinberg JB. Acute Myeloblastic Leukemia in Paroxysmal Nocturnal Hemoglobinuria: Evidence of Evolution from the Abnormal Paroxysmal Nocturnal Hemoglobinuna Clone. The Journal of Clinical Investigation 1987; 79(1): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC424052/ (accessed 08 April 2019).

13. Parker CJ. Paroxysmal Nocturnal Hemoglobinuria. https://rarediseases.org/rare-diseases/paroxysmal-nocturnal-hemoglobinuria/ (accessed 08 April 2019).

14. Risitano AM, Marando L, Seneca E, Rotoli B. Hemoglobin normalization after splenectomy in a paroxysmal nocturnal hemoglobinuria patient treated by eculizumab. Blood. 2008; 112(2): . http://www.bloodjournal.org/content/bloodjournal/112/2/449.full.pdf (accessed 08 April 2019).

15. Luzzatto L, Gianfaldoni G, Notaro R. Management of Paroxysmal Nocturnal Haemoglobinuria: a personal view. British Journal of Haematology. 2011; 153(): . https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-2141.2011.08690.x (accessed 08 April 2019).