Original Article

Bone Marrow Aspiration Cytology Studies In A Tertiary Hospital, Nigeria: A Serie Of 88 Cases

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ABSTRACT

Background: Bone marrow aspiration (BMA), an invasive test is crucial in evaluation of anaemias and other blood diseases, especially in situations where diagnosis remains cryptic after detailed clinical history, physical examination and peripheral blood analysis. BMA is performed by trained haematologists in the course of evaluating patients with primary or secondary haemopathies. However, there is sparse local data/report on its clinical utility. This study therefore assessed the common clinical indications, diagnostic findings and associated complications in our locality.

Methodology: A prospective cohort study of 88 cases of BMA procedures among patients managed and co-managed by the adult haematology unit at the University of Benin Teaching Hospital (UBTH), Benin City was carried out. Relevant demographic, clinical data and intra-procedure details were obtained using a structured questionnaire within 24 hours of the procedure during the study period through case file review and patient interview. Intra-procedure intensity was graded in patients above 14 years using numeric pain scale of 0 to 10. All patients were followed up for a period of 1 to 2 weeks post-procedure.

Result: The mean (SD) of the subject was 40 ± 24 years. Most (79.5%) of the BMA cytology were performed among adults (≥15 years of age), mostly on in-patient basis (86.4%). Posterior iliac crest was the most commonly used site (83%). Aspiration yield was adequate in 83% of cases. Mean intra-procedure pain score was 5.17 ± 2.01. Most common bone marrow diagnoses were combined (substrate) deficiency (26.1%), acute leukaemias (18.2%), pure megaloblastic anaemia (10.2%), malignant plasmacytosis (7.9%) and marrow carcinomatosis (7.9%). Pain was the most frequent complication, observed in 98.9% of cases.

Conclusion: BMA cytology is a highly informative/diagnostic test procedure performed by haematologists in evaluating blood and blood related diseases in our environment. BMA is relatively safe although significant procedure related pain was frequently reported. Efforts should therefore be directed at better analgesia. Patients with unexplained cytopenias and other relevant indications should be referred for haematology consultation and possible BMA.

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Introduction

Bone marrow aspiration (BMA) is an invasive procedure whereby representative specimen of spongy bone marrow is obtained through a needle aspiration for diagnostic evaluations especially cytology and stem cell harvest.[1-4] The history of in vivo bone marrow examination dates back to as early as 1876 when Mosler used a regular wood drill to aspirate bone marrow particles from a patient with leukaemia.[2] BMA still remains a veritable tool in the haematologist armamentarium for conducting diagnosis and differentiation of primary and secondary haemopathies. In today's practice, the clinical relevance of BMA goes beyond cytologic evaluation of haematopoietic and non-haematopoietic marrow cells. BMA specimens are useful in further diagnostic assays including cytochemical/special stainings, immunophenotyping, microbiologic tests, cytogenetic analysis and molecular studies.[1,2,5] Additionally, BMA is a major source of stem cells for haemopoietic stem cell transplantation.[3] Often, a trephine biopsy is carried out as part of the same procedure.[4]

The BMA procedure is performed by a qualified haematologist during clinical evaluation of patients with blood and blood related diseases. BMA is invasive and requires proper patient education and consent. Patients for BMA are carefully selected. Often times, patients with suspected marrow diseases whose diagnosis remains inconclusive after examination of the peripheral blood with full blood count (FBC), peripheral blood film (PBF) and ancillary tests, require BMA. Usually, BMA is engaged in cases of unexplained cytopenia (anaemia, leucopenia, thrombocytopenia), unexplained splenomegaly and lymphadenopathy, diagnosis of acute leukaemia, megaloblastic anaemia, plasma cell myeloma, myelophthisic anaemia, monitoring of success of cancer chemotherapy, staging of lymphoma and other solid tumors, staining for marrow iron stores and other cytochemistries, chromosomal studies/karyotyping and molecular genetic analysis.[1,2,5-8] Before a BMA is performed, clinical history and laboratory tests including FBC, reticulocyte count and PBF must be evaluated. A consultation for BMA is first a consultation to review the patient before the procedure is performed. Patient must be fit for the procedure haemostatically and otherwise. Performing a BMA must meet clear indications. Pre-procedure evaluation of the patient includes establishing clear indications, assessment of the patient's haemostatic status, patient education about the procedure and proper consent. Once the marrow blood is harvested under aseptic protocols, the smear is made, remaining specimen is stored in EDTA anticoagulant bottle and further processing is carried out in the haematology laboratory.[1] Well prepared marrow smears are viewed and reported by the haemato-morphologists. Reports are subsequently translated to patient care or dispatched to the requesting clinicians.[5]

Despite being a highly informative test procedure in diagnostic evaluation of blood and blood related diseases, there is sparse local literature on its indications, diagnostic utility/findings and complications of BMA in Nigeria. This study therefore evaluated and reports on the spectrum of common indications, bone marrow diagnosis and observed complications of the BMA among patients seen at UBTH, Benin City, Nigeria. This would also serve for possible comparison with findings from other parts of Nigeria and beyond.

Materials And Methods

This is a hospital based, prospective study conducted at the University of Benin Teaching Hospital (UBTH), Benin City. UBTH is a referral tertiary health institution located in Egor LGA along Lagos-Benin Expressway. The hospital has different medical and surgical sub specialties including haematology. The haematology unit is concerned with management of blood and blood related diseases, laboratory services, clinical interpretation of laboratory tests, consultations to other specialties.

BMA examinations are performed by the haematology team of the hospital in the course of her clinical duties and consultations on both own patients and referred patients. All the BMA examinations performed over a period of twelve months (between January 2014 and January 2015) were profiled using a structured, interviewer-administered questionnaire. Relevant clinical data of the patient, laboratory tests, intra- and post-procedure details were recorded. BMA were performed using a standard unit protocol as adapted from ICSH guidelines and other authorities.[1,5] Intra-procedure pain severity was quantified using a validated pain scale in all patients above 14 years of age.[9] Patients were followed up for a minimum period of 1week for post-procedure complications. Patients with known coagulopathies or thrombocyte counts less than 20,000/ul were deferred from the procedure until adequate blood component supports were given. Similarly, patients on anti-platelet medications were deferred for a few days. All BMA were performed after detailed explanation of the procedure to the patient and or parents and proper consent obtained.

All data were inputted and analyzed using Statistical Package for Social Sciences (SPSS) 16. Descriptive statistics were performed as appropriate. Level of association between sepsis and cytopenia was performed using chi square analysis. Association of intra-procedure pain severity scores with variables such as sex, aspiration site, number of aspirations, BMA with or without trephine

biopsy were tested using student T test or Analysis of Variance (ANOVA) as appropriate. Findings are presented in frequencies and tables. Statistical significance is set at probability level of 5% (i.e. p-value = 0.05)

Result

A total of 88 cases of BMA were profiled during the study period. Majority of the subjects (79.5%) were aged 15 years and above (Table 1). Mean (SD) age of the subjects was 40 ± 24 years with a male to female ratio of 1.05:1. Most BMA procedures (86.4%) were done on patients during admission, the remaining were performed on out-patient basis (Table 1). The blood cell counts of the patients were highly variable with a mean total white blood count of 23,500/ul, granulocyte count of 13,600/ul, platelet count of 152,000/ul and haematocrit of 23.02%. About 10% of the subjects had inter-current significant bleeding disorders (severe thrombocytopenia and coagulopathy) for which they were corrected and stabilized prior to the procedure (Table 1). Local anaesthesia with lidocaine was used in all patients. A few (3.4%) of the patients aged less than 15 years were sedated with promethazine/pentazocine combination in order to achieve better analgesia and patient cooperation (Table 2). Most of the aspirates (83%) were taken from the posterior iliac crest, the rest were taken from anterior iliac bone and femur in children less than 2 years (Table 2). Multiple aspirations were performed in about 16% of the subjects (Table 2). The most frequent indications for initiation of BMA studies were unexplained anaemia (46.6%), suspected leukaemias (17%) and monitoring of cytotoxic therapy success in treated cases (13.6%) (See Table 1). About 44% of the subjects had concurrent bone marrow aspiration and trephine biopsy, while the remaining had solely a BMA procedure. Indications for concurrent BM trephine included evaluation of marrow cellularity in suspected aplastic anaemia cases, dry tap/inadequate marrow yield to enable imprints and others (Table 2). Intra-procedure pain severity was observed to be 5.17 (total of 10). Mild non-opioid analgesia with paracetamol was the commonly prescribed post-procedure in 67% of the subjects (Table 3). The common marrow diagnosis (in order of decreasing frequencies) were combined (substrate) deficiency (26.1%), acute leukaemia (18.2%), pure megaloblastic anaemia (10.2%), malignant plasmacytosis (7.9%), marrow carcinomatosis (7.9%), chronic leukaemia (6.8%), marrow involvement by solid blood tumors such as non-Hodgkins' lymphoma (6.8%). No conclusive report was made in 4.5% of cases. The most frequently reported/observed post-procedure complications were local pain at the site of the procedure (98.9%) and local sepsis (3.4%) (Table 3). There is no significant association between leucopenia/granulocytopenia and sepsis in the studied population. However, septic complication was significantly associated with BMA procedures performed on outpatient basis (Table 4). The mean pain severity score was observed to be slightly higher in females, in-patients, use of the posterior iliac crest, multiple intra-procedure aspirations and trephine biopsy but were not statistically significant (Table 5).

TABLE 1A: PATIENT CHARACTERISTICS

Characteristics		Frequency (n)	Percentage (%)
Age (years)	< 15 years	18	20.5
	≥ 15 years	70	79.5
Mean ± SD = 40.07 ± 24.16, Median = 43, Minimum = 11 weeks, Maximum = 90 years			
Sex	Male	45	51.1
	Female	43	48.9
M : F Ratio: 1.05 : 1			
Location	In-Patient	76	86.4
	Outpatient	12	13.6
Bleeding Disorder	Thrombocytopenic	8	9.1
	Coagulopathy	1	1.1
	Nil	79	89.8

N = 88 (100%)

Table 1B Indications of Bone marrow aspiration

BMA indications	Frequency (n)	Percentage (%)
Unexplained Anaemia	41	46.6
Unexplained Leuco-/ Thrombocytopenia	2	2.3
Unexplained Pancytopenia	1	1.1
Suspected Leukaemia	15	17
Suspected Plasma Cell Dyscrasia	8	9.1
Monitoring Therapy	12	13.6
Staging/Diagnosis Of Lymphoma	2	2.3
Unexplained Spleen/ Lymphadenopathy	4	4.5
Others	3	3.4

	Min Value	Max Value	Median	Mean ± SEM
Total White Cell Count (/ul)	800	720000	6350	23500 ± 8713
Granulocyte Count (/ul)	200	573000	3050	13600 ± 6633
Platelet Count (/l)	20000	615000	120000	152000 ± 11050
Haematocrit (%)	6	46.8	21.8	23.02 ± 1.03

Table 2: Intra-Procedure Details

VARIABLES		Frequency (n)	Percentage (%)
Anaesthetic/ Sedative*	Lidocaine	88	100
	Promethazine	3	3.4
	Pentazocine	3	3.4
Aspiration Site	Anterior ilium	13	14.8
	Posterior ilium	73	83.0
	Sternum	-	-
	Femur	2	2.3
Number Of Aspiration Sites	Single	74	84.1
	Multiple	14	15.9
Aspiration Yield	Adequate	73	83.0
	Not Adequate	10	11.4
	Dry Tap	5	5.7
Trephine Biopsy	Yes	39	44.3
	No	49	55.7
Trephine Biopsy Indications	None	49	55.7
	Overall cellularity/suspected aplastic anaemia	8	9.1
	Dry Tap/Inadequate yield	7	8
	Others	18	20.5
	Not Clear	6	6.8
Pain Intensity	Not assessed**	18	20.5
	0 – 3 (mild)	18	20.5
	4 – 7 (moderate)	45	51.1
	8 – 10 (severe)	7	8.0
Mean Pain Score (±SD) = 5.17 ± 2.01			

N = 88 (100%), * multiple responses, **not assessed in children less than 15 years

Table 3: Post Procedure Findings

Variables		Frequency (N)	Percentage (%)
Analgesia	Nil	7	7.9
	Mild Non-Opioid	59	67.0
	NSAID	10	11.4
	Opioid	12	13.6
Diagnostic Findings*	Acute Leukaemia	16	18.2
	Malignant Plasmacytosis	7	7.9
	Haematologic Remission	2	2.3
	Relapse/Refractory Leukaemia	1	1.1
	Failed/Partial Induction	2	2.3
	Inconclusive/Not Diagnostic	4	4.5
	Marrow Carcinomatosis	7	7.9
	Marrow Infiltration Of Blood Cancers	6	6.8
	Combined (Substrate) Deficiency	23	26.1
	Chronic Leukaemia	6	6.8
	Megaloblastic Anaemia	9	10.2
	Myelodysplasia	1	1.1
	Suspected Aplastic Anaemia	3	3.4
	Others	4	4.5
Procedure Related Complications	Local Pain	87	98.9
	Haemorhage	2	2.3
	Local Sepsis	3	3.4
	Needle Breaks	1	1.1
	Haematoma	-	-
	Vascular Injury	-	-

N = 88 (100%), *multiple responses

Table 4: Association Between Sepsis And Cytopenia/ Patient Location

	LEUCOPENIA		p-Value
SEPSIS	YES	NO	
YES	1	2	0.620
NO	23	62	
GRANULOCYTOPENIA			
	YES	NO	
YES	1	2	0.688
NO	27	58	
Patient Location			
	IN-PATIENT	OUT-PATIENT	
YES	1	2	0.048
NO	75	10	

N = 88 (100%)

Table 5: Association Of Pain Severity Scores With Other Variables

VARIABLES		PAIN SCORE MEANS	SEM	p-value
Sex	**Male**	**5.09**	**0.36**	Df = 1, F = 0.112, p = 0.739
	Female	**5.25**	**0.32**	
Patient Location	**In patient**	**5.28**	**0.28**	Df = 1, F = 0.915, p = 0.342
	Outpatient	**4.67**	**0.33**	
BMA site	**Posterior ilium**	**5.28**	**0.28**	Df = 1, F = 0.915, p = 0.342
	Anterior Ilium	**4.67**	**0.39**	
Number of BMA aspirates	**Single**	**5.10**	**0.27**	Df = 1, F = 0.450, p = 0.505
	Multiple	**5.55**	**0.49**	
Trephine Biopsy	**Yes**	**5.21**	**0.34**	Df = 1, F = 0.024, p = 0.876
	No	**5.13**	**0.34**	

N = 70 (79.5% of total cases)

Discussion

Most cases of BMA studies were performed on in-patient basis, suggesting that most of the patients' symptomatology and their management required hospitalization. Clinically significant bleeding disease was observed in 10% of the cases, which is a relative contraindication to the procedure except corrections for thrombocytopenia or coagulopathy were made. Most of the aspirate specimens were taken from the posterior iliac crest, anterior ilium was less favoured. The sternum was totally avoided. This may be related to the possible fatal risk of damage to the great vessels during sternal puncture.[8,10] The tibia is the preferred site in children aged less than 18 to 24 months.[2,6,8] Cytopenias generally results from accelerated peripheral destruction of blood cells as in auto-immune disease, underproduction or maturation defects.[11] Most times, if the cause is not found peripherally, there is need for examination of the bone marrow, the site of haematopoiesis. It is therefore not surprising that unexplained cytopenia was the most frequent indication for bone marrow examination in the index study. BMA are carried out principally to permit cytologic evaluation of marrow cells (haemopoietic and non-haemopoietic). BMA specimens are also relevant for additional investigations including cytogenetic, molecular studies, flow cytometry/Immunophenotyping, cytochemistry, microbiological studies and others.[1,2,4]

Though a small series, this study however provides useful information on predominant causes of reticulocytopenic anaemia (bone marrow suppression) in this locality. Most common bone marrow diagnosis was combined (substrate) deficiency anaemia, observed in 26% of cases (see Figure 1). This is not unexpected as the most common cause of anaemia in a developing nation like Nigeria is reported to be nutritional deficiency.[12-14] This is comparable to a local report by Damulak et al, who reported the most frequent marrow diagnosis as nutritional deficiency anaemias in one-third of marrow aspirates, followed by leukaemias. [15] However, in another retrospective study of 185 BMA cytologies in Jos, Egesie et al observed acute leukaemias to be most common cause of anaemia in the locality followed by nutritional deficiency anaemias.[16] In this index study, diagnosis of acute leukaemias were the second most frequent diagnosis following bone marrow examination in some of the cases (see Figure 2). Similarly, in an Indian study, erythroid hyperplasia, acute leukaemias and megaloblastic anaemia were reported as the most common diagnostic findings.[17] The pattern of marrow diagnosis in a Ghanian study appears different from that observed in this index study, which reported lymphoma as the most frequent diagnosis.[18] Again, in a report from Saudi Arabia, the most common diagnoses encountered were acute leukaemia, immune thrombocytopenia, hypersplenism, chronic granulocytic leukaemia and megaloblastic anaemia.[19] These differences may be related to pattern of bone marrow requests, clinical indications for bone marrow evaluation and possible geographic difference in the patterns of marrow diseases. Other patterns of bone marrow diagnosis in the index study included marrow carcinomatosis and malignant plasmacytosis (Figures 3 and 4 respectively).

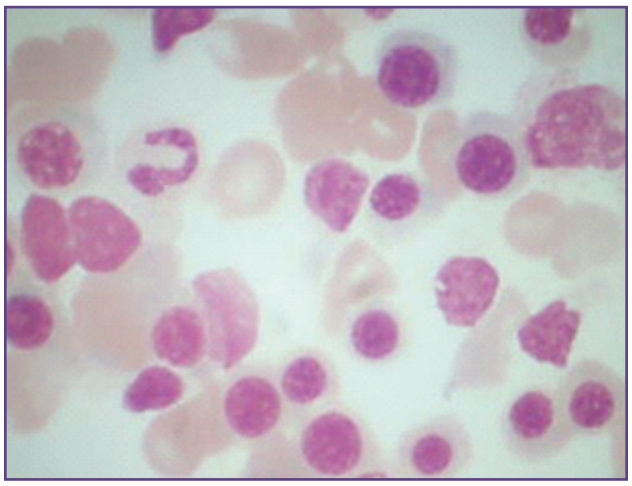

Fig. 1: Mixed deficiency anaemia. BMA smear shows erythroid hyperplasia with several late and intermediate megaloblasts and dying cells. Micronormoblasts were also present (Leishman stain X1000).

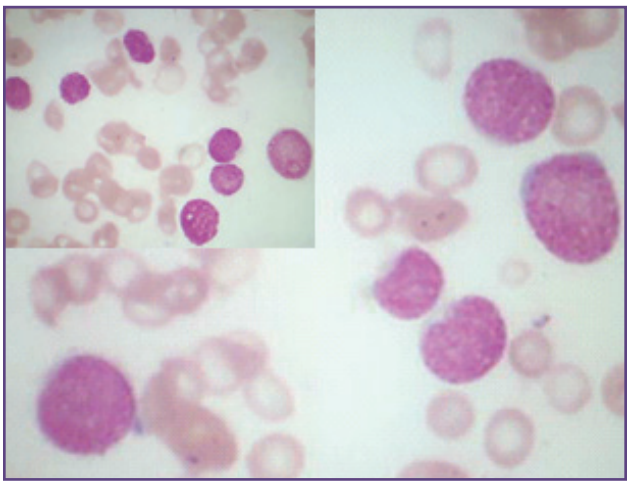

Fig 2: BMA cytology showing immature lymphoid cells (blasts) of varying sizes, high nuclear:cytoplasmic ratio, some with prominent nucleoi and occasional cytoplasmic vacuolations (see inset). Diagnosis: Acute lymphoblastic leukaemia FAB L2 (Leishman stain x1000, inset x400)

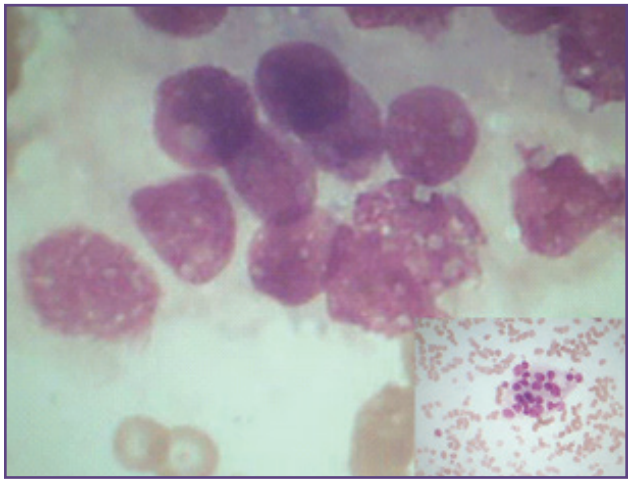

Fig 3: Marrow carcinomatosis. BMA smear shows a nest, cluster of pleiomorphic looking, non haematopoietic cells (see inset) (Leishman stain x1000, inset x100)

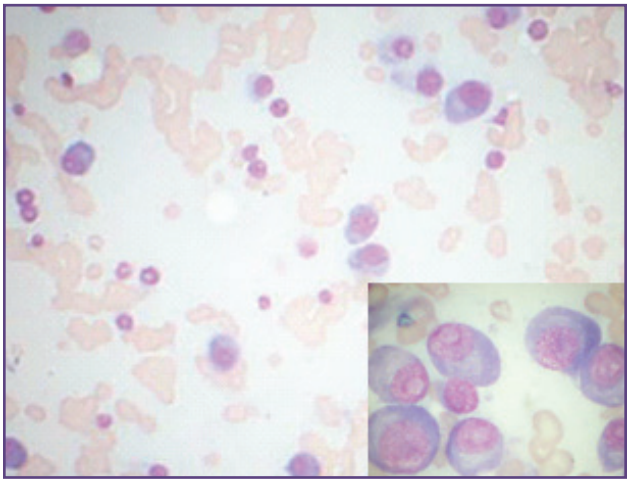

Fig 4. Malignant plasmacytosis. BMA showing crowding of the marrow by malignant plasma cells with features of increased peri-nuclear halo and prominent nucleoli (see inset). (Leishman stain x400, inset x1000)

Dry tap or inadequate aspirate yield, as observed in some of the cases, is an indication for trephine biopsy (TB).[14] TB allows for preparation of imprints and better assessment of overall cellularity, marrow architecture or infiltrations.[1,2,5] Dry taps are due to hypercellularity or fibrosis caused by the underlying disease or an inadequate technique.[1,5]

Pain was a main complication of BMA in this study and poor pain control may dissuade patients in event of a need for repeat procedures. Though 92.3% of the patient-cases received post-procedure analgesia, most of the analgesia (67%) was conducted with mild non-opioid (paracetamol). Non steroidal anti-inflammatory drugs (NSAIDS) were less frequently used possibly due to its propensity for platelet dysfunction. Marked variation in intra-procedure pain severity may be related to patient factors such as individual pain thresholds, anxiety and apprehensiveness, skills and expertise of the operator or the differing quality of the anaesthetic agent.

In a large series of over 50,000 cases, haemorhage and local infection were very rare. Fourteen cases had serious haemorhage with one death and six required transfusion. [20] In the index study, local sepsis occurred in a few

of the patients but was not found to be associated with/ related to leucopenia or granulocytopenia. BMA cases performed on outpatient basis were significantly associated with sepsis. The quality of post-procedure care including adherence to aseptic protocol in wound care/dressing may have a significant bearing on the incidence of septic complications among out-patients. Other complications such as neuropathy, osteomyelitis, needle breakages, vascular injury, fracture or mortality were either minimal or not present. Needle breakage occurred in one of the cases. This is possibly attributable to re-use of needles following requisite sterilizations.

Conclusion

BMA should be performed by a qualified haematologist who is conversant with the procedure and its potential complications. Bone marrow studies may be safely performed at platelet counts above 20,000/ul in the absence of platelet dysfunction. Preferably, BMA should be performed at platelet counts above 50,000/ul especially in patients with aplastic anaemia or platelet consumption diseases.[6,8,20]

To allay fears/anxiety and reduce procedure related pain, it is recommended that patients/candidates for bone marrow studies should be properly educated about the procedure, its indication and potential risks. Informed consent should be obtained and documented. Local anaesthesia should be allowed the minimum time of onset to take effect before the procedure. Additional skills such as oral analgesia may help with pain relief intra-procedure. BMA related analgesia should be individualized, tailored to individual needs, upon careful evaluation of prior analgesic history and co-morbidities, as pain severity and duration may be related more to the individual patient pain thresholds. Careful attention should be paid to adequate intra- and post-procedure analgesia.

BMA should not be a first line investigation. It is often indicated after initial evaluation of the peripheral blood and other ancillary tests, in patients with blood or blood related diseases. As such, patients with unexplained cytopenias should be referred to and co-managed with haematology team.

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Competing Interests

None declared

Reference

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