Asian Hematology Research Journal

Volume 6, Issue 4, Page 271-276, 2023; Article no.AHRJ.108960

Chronic Myelomonocytic Leukaemia (CMML) and Vasculitis: A Rare but Known Association

Yih Hoong Lee [a*], Shan Kai Ing [a], Jian Yuan Cheng [b], Kelly Kee Yung Wong [c] and Grace Wan Chieng Lee [d]

[a] Department of Medicine, Sibu General Hospital, Ministry of Health, Sibu, Sarawak, Malaysia.
[b] Department of Pathology, Sibu General Hospital, Ministry of Health, Sibu, Sarawak, Malaysia.
[c] Department of Radiology, Sibu General Hospital, Ministry of Health, Sibu, Sarawak, Malaysia.
[d] Department of Medicine, Division of Haematology, Sarawak General Hospital, Ministry of Health Malaysia, Kuching, Sarawak, Malaysia.

Authors' contributions

This work was carried out in collaboration among all authors. Author YHL initiated the idea for case reporting and prepared the final copy of manuscript with author SKI. Author GWCL is the managing haematologist. Author JYC is the hematopathologist analysing all the BM specimens. Author KKYW is the radiologist interpreting all the imaging for this case. All authors had read and approved the manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/108960

Case Study

Received: 15/09/2023
Accepted: 19/11/2023
Published: 22/11/2023

ABSTRACT

Aims: To illustrate the relationship between Chronic Myelomonocytic Leukaemia (CMML) and Systemic inflammatory and autoimmune diseases (SIADs).
Presentation of Case: This report presents a case of a 68-year-old gentleman with newly-diagnosed CMML with SIADs. The diagnosis of CMML was confirmed with bone marrow examination findings and a negative BCR-ABL fusion gene. During hospitalization, the patient developed painless right inguinal swelling. Urgent imaging revealed focal arteritis of the right distal external iliac/proximal common femoral artery and a small focal dissection of the infrarenal

**Corresponding author: E-mail: yihhoong1992@gmail.com;*

abdominal aorta. However, he was asymptomatic and reported no other connective tissue disorder symptoms. He was started on cytoreductive therapy for CMML and was treated conservatively for the arteritis and dissection of the infrarenal abdominal aorta. A follow-up scan revealed resolution of arteritis.

Discussion: Chronic myelomonocytic leukaemia (CMML) with systemic inflammatory and autoimmune diseases (SIADs) is rare. The mainstay of treatment is corticosteroids, immunosuppressants, and, most importantly, treating the underlying cause.

Conclusion: This case highlighted the importance of recognizing the possible SIADs associated with CMML. Treating the CMML might lead to resolution of SIADs.

Keywords: Chronic myelomonocytic leukaemia; systemic inflammatory and autoimmune diseases; vasculitis; cytoreduction.

ABBREVIATIONS

CMML : Chronic Myelomonocytic Leukaemia
SIADs : Systemic Inflammatory and Autoimmune Diseases
WHO : World Health Organization
MDS/MPN : Myelodysplastic Syndrome/Myeloproliferative Neoplasm
FBP : Full Blood Picture
NGS : Next-Generation Sequencing
USG : Ultrasound
CTA : Computed Tomography Angiography
ANA : Antinuclear Antibody
dsDNA : Double Stranded DNA
ENA : Extractable Nuclear Antigen
ANCA : Antineutrophil Cytoplasmic Antibody
BM : Bone Marrow
AML : Acute Myeloid Leukaemia
HSCT : Haematopoietic Stem Cell Transplantation
HMA : Hypomethylating Agent

1. INTRODUCTION

CMML is a rare form of haematological malignancy. According to World Health Organization (WHO) revised classification in 2016, it is classified as myelodysplastic syndrome / myeloproliferative neoplasm (MDS/MPN) [1]. SIADs, including large vessel vasculitis, have been reported in 20% patients with CMML [2]. We reported a case of newly-diagnosed CMML associated with focal dissection of the infrarenal abdominal aorta and focal arteritis of the external iliac/common femoral artery. This case highlighted the importance of a high index of clinical suspicion of SIADs in newly diagnosed CMML/MDS patients.

2. PRESENTATION OF CASE

A 68-year-old Chinese man, an ex-smoker who was previously healthy, presented to us with one-month history of lethargy and abdominal discomfort associated with early satiety. He was unemployed and had no known family history of malignancy. Physical examination revealed a medium-built man with normal vital signs. There were conjunctival pallor and moderate splenomegaly approximately 4cm below costal margin. Otherwise, he has no clinical features suggestive of haemolytic anaemia nor having any lymphadenopathies. Initial laboratory tests revealed hyperleukocytosis (total white count of 339.9 x 10^9/L) with monocytosis (11.7 x 10^3/mm), as well as anaemia and mild thrombocytopenia (haemoglobin 8.3g/dL, platelet count 129 x 10^9/L). A full blood count picture (FBP) showed 25% monocytes with 2% blast cells (promonocytes) (Figs. 1, 2). A bone marrow examination was performed, and the result was consistent with the diagnosis of CMML-1 (persistent monocytosis >10% in FBP, <20% blast in FBP and bone marrow with presence of trilineage dysplasia, negative BCR-ABL1). However, there were no cytogenetic abnormalities detected and next-generation sequencing (NGS) was not performed as it was not available in our centre.

Full Blood Picture Images

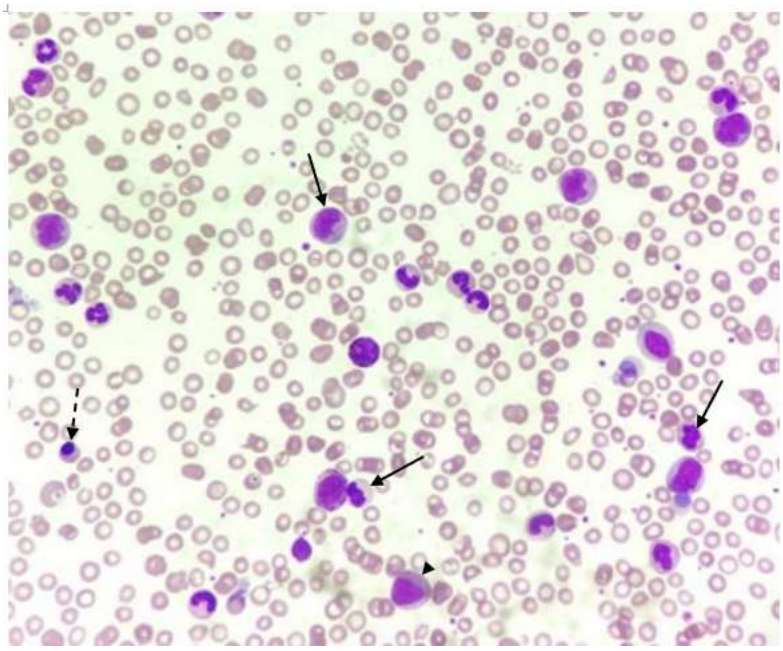

Fig. 1. PBF shows neutrophilia and monocytosis. Dysplastic neutrophils with hyposegmentation and hypogranulation are seen (black arrow). A nucleated red cell (dashed arrow) and a myelocyte (arrowhead) are shown

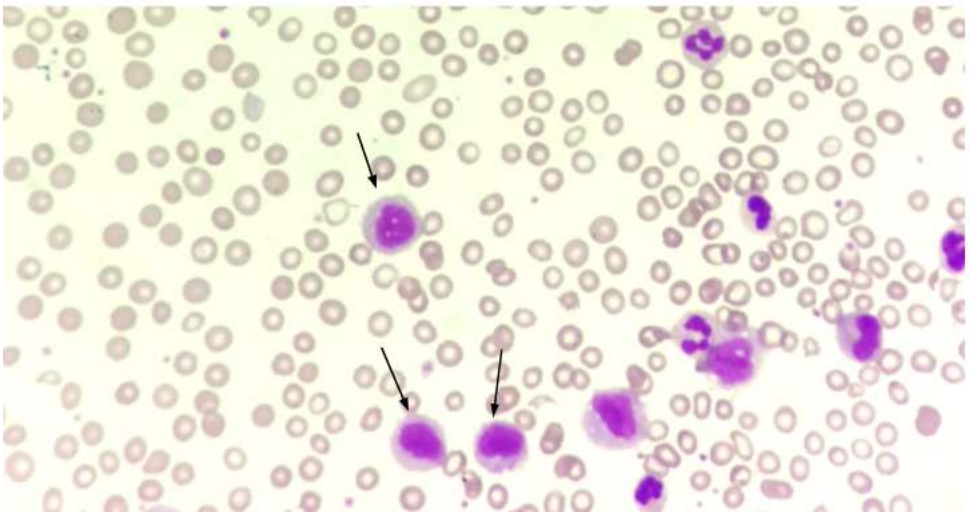

Fig. 2. This figure shows monocytes with a few showing abnormal lobulation (black arrow). Macrocytes are prominent in the background red cells

The clinician incidentally noted a pulsatile right inguinal swelling of unknown duration during hospitalization. Clinically it was a painless, pulsatile and expansile swelling. The distal pulses in the lower limbs were present with good volume. Urgent ultrasound (USG) of the right inguinal region revealed focal segmental wall thickenings with soft tissue echogenicity involving the right external iliac artery and right common femoral artery (Fig. 3a, b). Computed tomography angiography (CTA) of the aorta and bilateral lower limbs was performed. It was reported as a small focal dissection in the infrarenal abdominal aorta at the L3 level with no evidence of leakage and focal arteritis of the right distal external iliac/proximal common femoral artery (Fig. 4a, b). Urgent vascular surgeon consultation was sought, and the patient was managed conservatively in view of no evidence of leaking.

Radiological Images

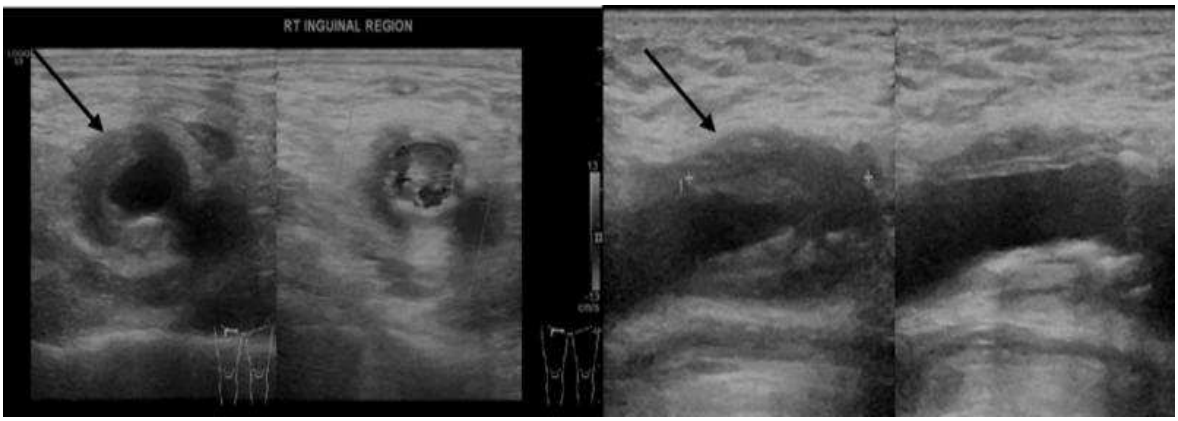

Fig. 3a **Fig. 3b**

Fig. 3a, 3b. Initial ultrasound finding of the right inguinal swelling on transverse (3a) view and longitudinal (3b) view shows focal area of wall thickenings (black arrows) associated with surrounding soft tissue echogenicity involving the right external iliac artery, which is confirmed on CT angiogram

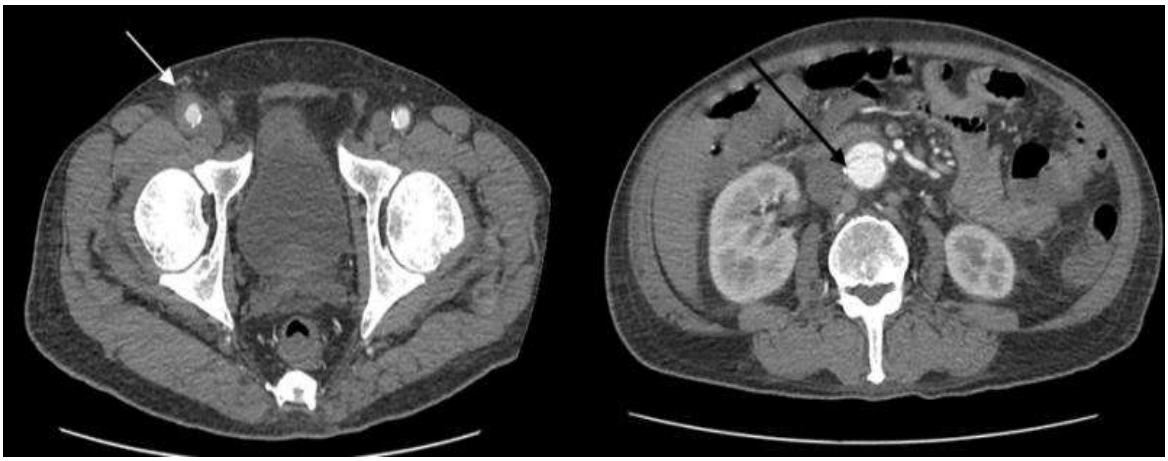

Fig. 4a **Fig. 4b**

Fig. 4a, 4b. CT angiogram of the aorta shows circumferential eccentric thickening with enhancement of the vessel wall (white arrow in Figure 4a) at the distal right external iliac artery extending to the proximal common femoral artery. Focal intimal flap at the anterior wall of the infrarenal abdominal aorta at L3 level (black arrow in Figure 4b) is suggestive of focal aortic dissection

The patient did not exhibit other connective tissue disorder symptoms. Biohazard screening revealed positive Hepatitis B core antibody with undetectable Hepatitis B viral load level and negative Hepatitis C and HIV screening. Tuberculosis workup, including sputum TB GeneXpert, were negative. In addition, vasculitis workup, including ANA, dsDNA, ENA and ANCA were all negative. He was commenced on cytoreductive therapy with hydroxyurea without corticosteroid. Repeated USG 3 weeks post-cytoreductive therapy demonstrated resolution of focal arteritis of the right external iliac and common femoral artery (Fig. 5). Currently, he is

followed up closely in a haematology clinic. Hyperleukocytosis has significantly reduced (total white count of 119 x 10^9/L) after initiation of hydroxyurea. However, he requires regular blood transfusion fortnightly. There are no recurrence of signs and symptoms suggestive of SIADs.

3. DISCUSSION

CMML is a heterogeneous condition with both myelodysplastic and myeloproliferative features. It is more common in the elderly and shows a male predominance. Diagnosis of CMML can be made through peripheral blood tests, bone marrow examination, chromosomal analysis, and genetic tests. Unlike BCR-ABL1 rearrangement in CML, CMML has no pathognomonic findings [3]. CMML can be classified into three subtypes (WHO revised classification 2016) according to the percentage of blast cells (myeloblasts, monoblasts and promonocytes) in peripheral blood (PB) and bone marrow (BM). Second classification includes proliferative or dysplastic type according to total white count in peripheral blood. Close monitoring is needed as CMML patients pose a risk of transforming into Acute Myeloid Leukaemia (AML) [4].

SIADs have been reported in 20% of patients with CMML, especially CMML-1 [2,5]. However, the causal relationship between CMML and SIADs is unclear. The common SIADs include systemic vasculitis, arthritis, psoriasis, serositis, and chronic inflammatory demyelinating polyneuropathy [6] According to 2012 Revised International Chapel Hill Consensus Conference on Nomenclature of Vasculitides, systemic vasculitis of medium-sized vessels such as polyarteritis nodosa (PAN) and large-sized vessels such as giant-cell arteritis and Takayasu's disease are more likely associated with CMML [7].

Mainstays of treatment for CMML include cytoreductive therapy, hypomethylating agents (HMA), and haematopoietic stem cell transplantation (HSCT). Novel therapeutic agents are still under research and not in clinical practice yet [3]. Initiation of CMML treatment is based on appropriate risk classification. Asymptomatic patients with CMML-0 may be followed up until disease progression or until clinically significant symptoms develop. CMML patients with SIADs are generally treated with corticosteroids and immunosuppressants. However, steroid dependence and relapses remain an issue. Additional immunosuppressive therapy may further worsen cytopenia, which may lead to infection. Nevertheless, the usage of HMAs shows positive results in reducing dependency on steroids [6].

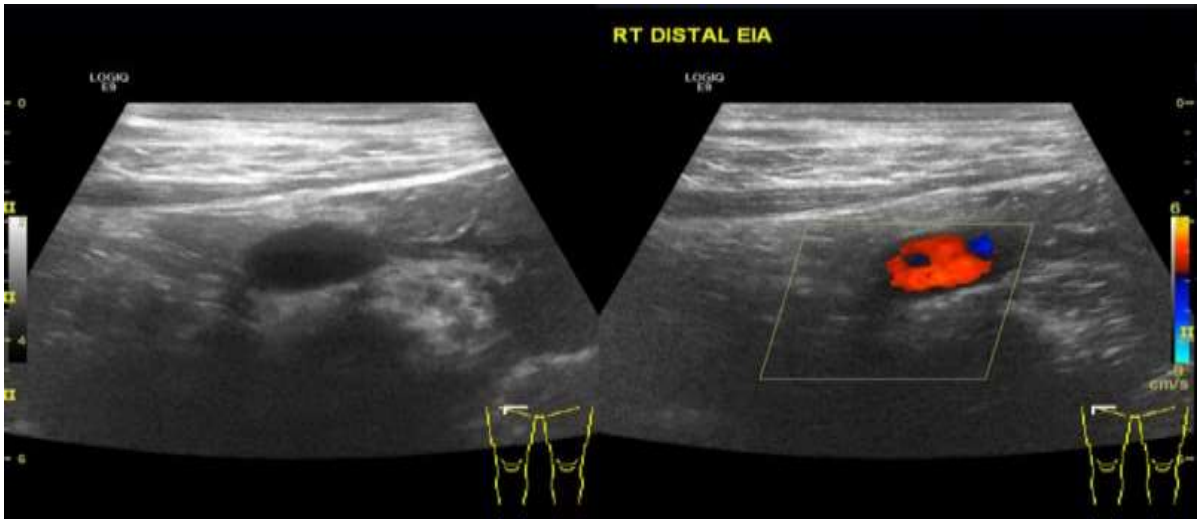

Fig. 5. Follow up ultrasound of the right inguinal region shows resolved wall thickening of the right external iliac artery

This patient was diagnosed with CMML-1 proliferative type based on WHO classification, with concurrent large-vessel vasculitis. After initiation of cytoreductive therapy, the vasculitis resolved spontaneously. Therefore, this case demonstrated that CMML is likely the antecedent entity and driver of SIADs, and that SIADs may improve or even resolve with the treatment of CMML. It is postulated that myeloid malignancies might trigger a cascade of inflammation leading to SIADs, which was reflected in this case. Since not all CMML patients require treatment, it is crucial to identify the presence of SIADs, which will influence the management of CMML.

4. CONCLUSION

SIADs associated with CMML are uncommon. The current knowledge regarding CMML with or without SIADs is extracted from studies conducted with small numbers of CMML patients. Further research and studies are required to better understand this disease and its association with SIADs in generating effective treatment modalities.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images and videos.

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health Malaysia for his permission to publish this article. No funding was received for the publication of this case report.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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DOI:10.1007/s11864-018-0581-6

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/108960