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Case Report: Giant Cell Arteritis, a Para-Neoplastic Manifestation of Acute Myeloid Leukemia

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ABSTRACT

We present a case of a previously healthy 61 year old female with a new diagnosis of Giant Cell Arteritis (GCA), initially treated with prednisone. One month later, she receives the diagnosis of Acute Myeloid Leukemia for which she gets a course of 7+3 induction chemotherapy. Clinicians need to be aware that large vessel vasculitis can be the first sign of a para-neoplastic syndrome related to a hematological malignancy. It has been hypothesized that blood malignancies such as leukemia are associated with depletion of the T-regulatory cells and overproduction of IL-6 and TNF-alpha. More research will need to be conducted in order to determine the relationship between GCA and DNA mutations such as in clonal hematopoiesis of indeterminate potential.

Keywords: Acute myeloid leukemia; Giant cell arteritis

INTRODUCTION

Hematological malignancies have been described to be associated with para-neoplastic syndromes. In fact, up to 10%-30% of patients who have myelodysplastic syndrome (MDS) present with autoimmune disease. This includes systemic vasculitis, arthritis, organizing pneumonia, glomerulonephritis, connective tissue disease, and neutrophilic dermatitis. The most common types of MDS-related vasculitides are giant cell arteritis (GCA) and polyarteritis nodosa. These autoimmune diseases usually develop months to years after the blood malignancy diagnosis. In the case of para-neoplastic GCA in the context of MDS, patients tend to develop milder symptoms (less jaw claudication and headache). We here report a case of para-neoplastic giant cell arteritis in the context of a newly diagnosed acute myeloid leukemia [1,2].

CASE PRESENTATION

A 61 year old female, previously healthy, presented herself to the emergency room with a two week history of retrosternal chest pain radiating to the back in between the scapulae. She was also complaining of significant night sweats. Upon arrival, her CRP was elevated to 169. A CT scan of the chest was done which showed mild wall thickening with abnormal adjacent fat stranding involving the transverse thoracic aorta, concerning for aortitis (**Figures 1 and 2**). The patient was seen by the rheumatology service. Given her age, she was thought to most likely have giant cell arteritis. The patient was initiated on prednisone 60 mg PO die. Four days later, she underwent a PET scan which demonstrated a low grade radiotracer accumulation in the ascending and transverse aorta, suspicious for low grade arteritis. An ultrasound of the temporal arteries was also done which came back negative. A basic immunologic workup was sent. The Anti-PR3, Anti-MPO, Anti-RO, Anti-LA, Anti-Smith Ab and Anti-RNP Ab came back negative while the ANA came back positive at a titer of 1:160. The patient had a good clinical response to steroids. She was discharged and followed by rheumatology as an outpatient. One month later, during her subsequent outpatient follow up in the rheumatology clinic, her prednisone was tapered and she was started on methotrexate. She was also found to have a gradual worsening of leukocytosis (WBC 15). The following month, she had abnormal CBC results: WBC 73, monocytes 59, Plt 41, and Hgb 95 g/L. A manual differential was done which showed 55 × 109 (75%) circulating blasts. The

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patient was sent to the emergency room. She was seen by the hematology service and had a bone marrow biopsy. She was diagnosed with Acute Myeloid Leukemia (intermediate to high risk: FLT3-ITD positive, NPM 1 mutated and DNMT3A mutated). During her admission to the hematology ward, she received 7+3 induction chemotherapy (cytarabine and idarubicin) with midostaurin. Her methotrexate was subsequently stopped due to drug-drug interaction and the prednisone was gradually discontinued. She is currently in remission. She is awaiting consolidation chemotherapy and allogeneic stem cell transplantation.

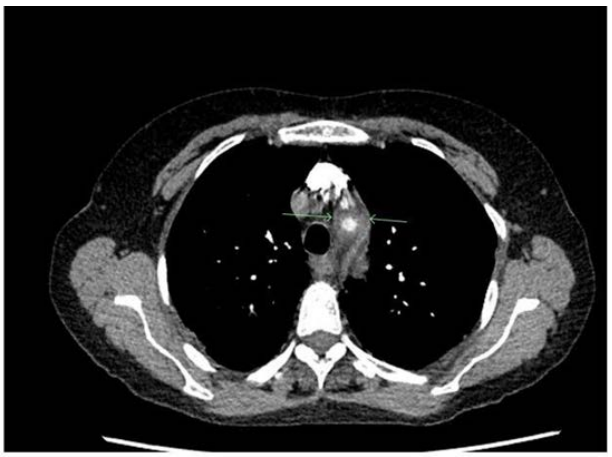

Figure 1: The green arrows point towards the vascular wall thickening and adjacent fat stranding of the transverse thoracic aorta. Radiological findings are suggestive of aortitis.

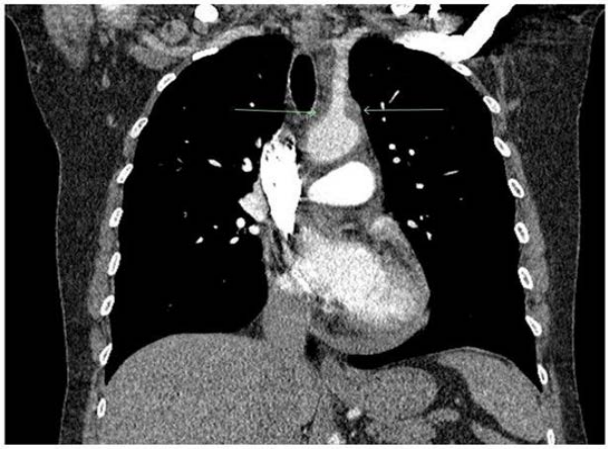

Figure 2: The green arrows point towards the vascular wall thickening and adjacent fat stranding of the transverse thoracic aorta. Radiological findings are suggestive of aortitis.

DISCUSSION

Acute Myeloid Leukemia (AML) is an aggressive blood cancer which causes the myeloid precursor cells to proliferate and invade the bone marrow. It is associated with more than 20% blasts on bone marrow biopsy. This results in abnormal and immature blood cell formation. Patients with AML are at higher risk of infection due to neutropenia, bleeding due to thrombocytopenia, weakness and dizziness secondary to anemia. Giant cell arteritis is a large vessel vasculitis which typically occurs in women above the age of 50. It is usually associated with headache, scalp tenderness, jaw claudication, chest and back pain. There is also a strong association with polymyalgia rheumatica. In this case, the diagnosis of giant cell arteritis preceded the diagnosis of AML by 1-2 months. Acute myeloid leukemia is associated with genetic mutations which can lead to immune dysregulation. It has been hypothesized that blood malignancies such as MDS and leukemia are associated with depletion of the T-regulatory cells which are responsible to control the immune response to self. Interestingly, blood malignancies such as MDS/AML are also associated with overproduction of certain cytokines such as IL-6 and TNF-alpha, which have a myelosuppressive effect and are associated with autoimmune diseases. This may explain the correlation between various autoimmune diseases such as vasculitis [3].

There has been several case reports of biopsy-proven GCA associated with AML. In addition to this, a longitudinal cohort study with 35 918 participants published by Ji and al. in the Oxford Rheumatology Journal in March 2010 using Swedish nationwide database demonstrated that there is an increased incidence of skin malignancy (melanoma and squamous cell carcinoma) and leukemia in patients hospitalized with polymyalgia rheumatica and/or giant cell arteritis. The Standardized incidence ratios of AML in the studied population with GCA/PMR were 2.15. Another retrospective study published by Loizon and al. in the Journal of Rheumatology in August 2006 had concordant results. In fact, of the 271 patients with temporal arteritis (TA) in the context of GCA, 20 of them had a concurrent malignancy which was diagnosed on average within 3.5 months. In 45% of the cases, the TA was related to blood cancer, particularly MDS. These paraneoplastic vasculitides had a good response to steroids [4-7].

Some studies have been trying to find a correlation between vasculitis such as giant cell arteritis, Takayasu arteritis, and ANCA-associated vasculitis and clonal hematopoiesis. Clonal hematopoiesis of indeterminate potential is cells that have acquired DNA mutations that have caused them to expand [8].

They are found in 10% of patients older than 65. These cells can acquire other mutations, particularly in TET2 and DNMT3A genes which play a key role in cytosine methylation and cancer development. CHIP mutations are associated with a ten-fold increased risk of transforming into blood malignancies such as AML/MDS. Clonal hematopoiesis of indeterminate significance has also been associated with vascular wall inflammation and premature atherosclerotic and cardiovascular disease [7]. In a study published in Haematologica in June 2020, the prevalence of CHIP in patients with ANCA-associated vasculitis was higher than the healthy control group of similar age (30.4% vs. 13.5%, $P< 0.001$). More research will need to be conducted in order to determine the relationship between clonal hematopoiesis and vasculitis [8,9].

CONCLUSION

In summary, this literature review suggests a real association between acute myeloid leukemia and giant cell arteritis. Clinicians need to be aware that large vessel vasculitis can be the first sign of a para-neoplastic syndrome related to a hematological malignancy. Future studies need to be conducted in order to better understand the pathophysiology of these autoimmune diseases, and in particular it will be essential to determine whether particular mutations predispose the patients to have vasculitis associated with AML. It will also be relevant

to determine if autoimmune diseases related to blood malignancy are associated with a worse clinical outcome and if these patients should undergo a different type of therapy.

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CONFLICTS OF INTEREST

The Authors declares that there is no conflict of interest.

ETHICS APPROVAL

Not applicable

CONSENT TO PARTICIPATE

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WRITTEN CONSENT FOR PUBLICATION

Informed consent was obtained for publication.

AVAILABILITY OF DATA AND MATERIAL

Not applicable

CODE AVAILABILITY

Not applicable

AUTHORS' CONTRIBUTIONS

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