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CASE REPORT

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G-CSF-induced TIPIC syndrome and large vessel vasculitis: A case report

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Key Clinical Message

We report a rare adverse event of transient perivascular inflammation of the carotid artery syndrome induced by granulocyte colony-stimulating factor injections. Recognition of this syndrome is important for physicians, to avoid the exposure of the causative medication, rule out differential diagnosis and delay the use of corticosteroids given the spontaneous improvement after discontinuation of the causative medication.

Abstract

A 73 year-old Caucasian woman presented with odynophagia, carotidynia, and fever 5 days following a granulocyte colony-stimulating factor (G-CSF) injection for chemotherapy-induced neutropenia in the setting of myelodysplastic syndrome. Examination showed painful swelling of the neck. Lab results showed inflammation with CRP 328 mg/L. A CT-scan revealed tissue infiltration thickening surrounding the left internal carotid artery, the carotid bifurcation, and the common carotid artery, as well as circumferential thickening of the aortic arch. Ultrasound of the left internal carotid artery found isoechoic wall thickening. Symptoms drastically improved without steroids in a short time period. Horton's disease, Takayasu's diseases, and infectious vasculitis were not retained due to the short time delay of symptoms onset, atypical echogenicity, and spontaneous improvement. A diagnosis of G-CSF-induced large vessel vasculitis transient perivascular inflammation of the carotid artery (TIPIC) syndrome was made. Seven days later, ultrasound control showed diminished thickening infiltration. G-CSF TIPIC is a rare adverse event that should be kept in mind in patients under G-CSF.

KEYWORDS

carotidynia, Fay's syndrome, G-CSF, TIPIC syndrome

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1 | INTRODUCTION

Carotidodynia or Fay' syndrome is characterized as neck pain near the carotid bifurcation.[1] Three main differential diagnoses can be responsible for carotidodynia: carotid dissection, cervical osteoarthritis, and large vessel vasculitis, that is, Takayasu disease and giant cell arteritis. The definition of carotidodynia has evolved in the past century: initially classified in the International Classification of Headache Disorders (ICHD) in 1988 and then declassified due to unspecific clinical signs in 2004.[2]

Over the last decade, reports of perivascular inflammation of the carotid artery have been described in patients with neck pain called TIPIC syndrome: transient perivascular inflammation of the carotid artery. The diagnostic criteria for this rare vascular disorder were established by Lecler et al. in 2017: acute neck pain directly around the level of the carotid bifurcation, eccentric pericarotidian infiltration on imaging, exclusion of another vascular or non-vascular diagnosis with imaging, and improvement within 14 days either spontaneously or with anti-inflammatory treatment. A recent multicenter retrospective study of 72 patients with TIPIC syndrome confirmed the benign nature of this disorder and that recurrence may occur in up to 20% of cases.[3] However, TIPIC pathophysiology and triggers remain poorly understood.

We report herein the case of a myelodysplastic syndrome (MDS) patient with granulocyte colony-stimulating factor (G-CSF) induced TIPIC syndrome.

2 | CASE PRESENTATION

A 73-year-old Caucasian woman with a past medical history of mammectomy for in situ breast cancer, appendectomy, and spinal angioma presented to her hematologist for consultation in February 2022 with acute carotidynia, left otalgia, and fever. She had been diagnosed with intermediate-2-risk MDS, and she had therefore started treatment with hypomethylating agents (chemical analog of cytidine, AZACYTIDINE) with complete remission obtained 6 months thereafter. Progression of MDS with 8% of blasts in the bone marrow in January 2022 led to the addition of an inhibitor of BCL-2 protein (VENETOCLAX) in association with AZACYTIDINE that was still ongoing. She was diagnosed with SARS-COV2 infection on February 04, 2022, with cough and rhinitis without any fever. Since this was an immunocompromised patient, we treated this pauci-symptomatic SARS-COV2 infection (without the need for oxygen therapy) with an intravenous infusion of sotrovimab 500 mg on February 05, 2022. She already received oral amoxicillin 1 g twice per day prescribed by her general practitioner on February 04, 2022, and then the treatment was stopped the following day. On February 08, 2022, the patient displayed deep neutropenia (290/mm^3) without fever and was treated with G-CSF (NIVASTIM) for 4 days.

Before those events, the last injection of AZACYTIDINE was performed on January 18, 2022, and the last dose of VENETOCLAX was taken on January 26, 2022. COVID-19 PCR test remained positive.

Odynophagia started February 10th, followed by left carotidynia on the 12th with swelling of the neck. Probabilistic antibiotherapy with macrolids was started on the 16th in the hypothesis of an ear, throat, and nose (ENT) infection with no improvement. At her hematology consultation on February 18th, patient displayed fever at 38.5°C and elevation of the C-reactive protein at 328 mg/L (Figure 1). A computed tomography (CT) scan performed the same day revealed tissue infiltration thickening surrounding the left internal carotid artery, the carotid bifurcation, and the common carotid artery, as well as circumferential thickening of the aortic arch (Figure 2). Cervical ultrasound confirmed perivascular infiltration, maximum next to the internal carotid bifurcation/external as well as a harmonious left peri-carotid circumferential thickening. In the more anterior fat/region of cervical group II A, there was a well-differentiated node, not suspicious. After disinfection, cytopunctures (2 passages) in the inter carotid region was performed. Cytology analysis

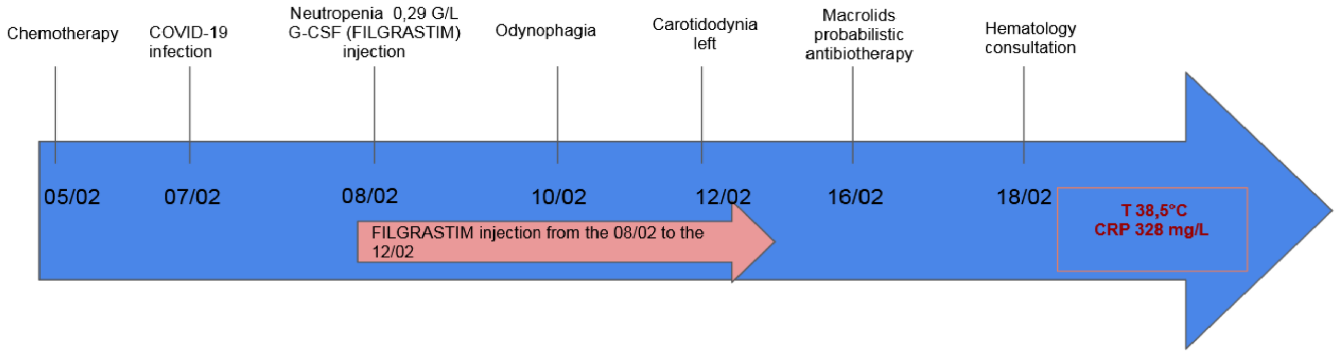

FIGURE 1 Symptoms timeline.

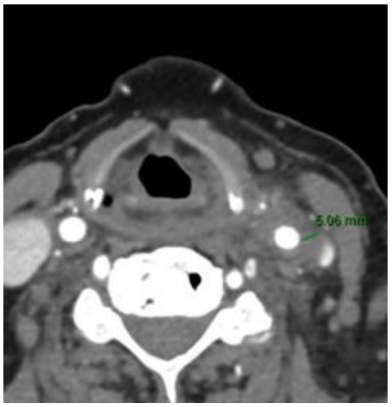

FIGURE 2 Computer tomography scanner showing tissue infiltration thickening surrounding the left internal carotid artery.

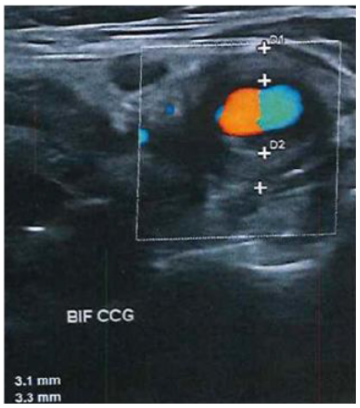

FIGURE 3 Ultrasound showing isoechoic wall thickening of the left carotid artery.

found a largely hematic material consisting sheets of red blood cells associated with some figured elements of the blood, polynuclear, and lymphocyte. No giant cell was visualized. No clearly identifiable tissue fragment was observed. No element of suspicious character was observed within the limits of these documents. The patient was transferred the same day to our internal medicine and vascular department.

Hypothesis of an infectious disease led to probabilistic broad-spectrum beta-lactam antibiotics. Examination revealed painful swelling of the neck with tenderness over her left carotid but had no vascular bruit. Another hypothesis was a large vessel vasculitis associated to MDS. Temporal arteries were normal, and she had no headaches. Arthralgias and blood pressure was symmetrical.

Oral cavity examination was normal. There were no thyroid nodules. Pulmonary and heart auscultation were normal. There were no skin rashes.

Ultrasound of the left internal carotid artery found isoechoic, circumferential wall thickening extending

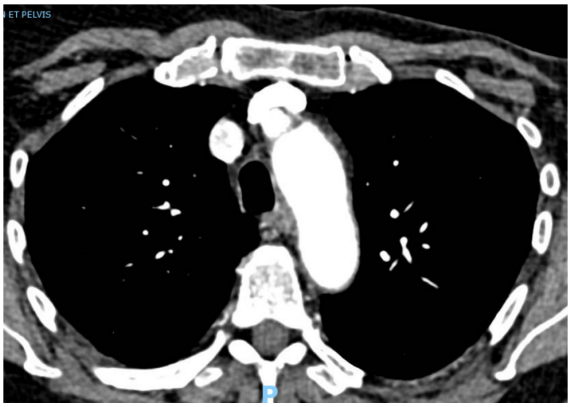

FIGURE 4 Computer tomography scanner showing clear regression of the periaortic infiltration at the level of the aortic arch.

to the origins of the internal and external carotid arteries (Figure 3). There were no inflammatory halos of the temporal arteries. The 18-FDG-TEP scanner showed hypermetabolism of the left carotid, circumferential hypermetabolism of the aortic arch, and moderate hypermetabolism of the anterior wall of the aorta of its transdiaphragmatic passage.

Blood cultures and mycobacterial blood cultures were sterile. EBV-specific serology showed past infection. HIV, HVC, HVB, and syphilis serologies were negative. Increased alpha-1 and alpha-2 were detected on protein electrophoresis. Determination of immunoglobulins and subclasses was normal. Serum complements C3 and C4 was normal.

Inflammatory syndrome decreased as well as neck tenderness. It was decided not to introduce steroids due to spontaneous evolution. Broad spectrum antibiotics were stopped after 5 days. Seven days later, ultrasound control showed diminished thickening infiltration. One and half month later (45 days later) in April 2022, CT scanner (Figure 4) and ultrasound showed clear regression of the periaortic infiltration at the level of the aortic arch and the isthmus but persistent periaortic thickening of the descending aorta. C-reactive protein returned to normal.

Hematologists collegially decided a therapeutic pause due to recent events with no reintroduction of azacytidine, venetoclax, or filgrastim. After 6 months of follow-up, she remains free from disease progression with persistent asymptomatic moderate bicytopenia (neutrophils 1200/mm^3, platelets 40,000/mm^3).

3 | DISCUSSION

We report a case of TIPIC syndrome induced by G-CSF injection. Transient perivascular inflammation of the carotid artery syndrome is a rare and newly clinically-radiologic

entity characterized by neck pain near the carotid area. To our knowledge, this is the first report of a TIPIC syndrome related to G-CSF. G-CSF was prescribed in the setting of a grade IV neutropenia related to MDS treatment. Recognition of this syndrome is important for physicians who must avoid the exposure of the causative medication. It is a serious condition that requires prompt diagnosis, and it may result in complications such as arterial wall dissection. Physicians should delay the use of corticosteroids given the spontaneous improvement of the carotid inflammation in most cases after discontinuation of the causative treatment.[1]

Four diagnostic criteria are necessary for the diagnosis of TIPIC[4]: occurrence of pain in the area of the carotid bifurcation, of acute onset (1), visualization of perivascular infiltrative tissue on imaging (2), exclusion of different vascular or nonvascular entities based on imaging findings (3), and improvement of clinical and imaging findings within 2 weeks spontaneous or with the use of anti-inflammatory medication (4). Our patient met the four criteria. Comparatively to the population described by Lecler et al., our patient was older (73 years old compared to the median age of 48 years old) and did not have any vascular risk factor or an autoimmune disease. Our patient presented with acute neck tenderness with a delay of 6 days between onset of symptoms and first imaging, similar to the description of Lercler's patients.

The physiopathology of TIPIC syndrome remains unknown. The main hypothesis is vascular proliferation with fibroblasts and chronic active inflammation. Neutrophils are known to have a role in regulation of inflammatory pathways, notably by the production of PGE2. G-CSF is a myeloid growth and differentiation factor, promoting neutrophils. It has been described in rheumatoid arthritis that G-CSF plays a role in precipitating and exacerbating, as well as in other inflammatory disorders.[3] We hypothesized that the injections G-CSF promoted neutrophils, with massive flow and infiltration of neutrophils with recruitment of inflammatory cells leading to perivascular infiltration and inflammation. The CRP levels are usually normal in TIPIC syndrome, contrarily in our case where CRP levels were highly elevated. This can be explained by the inflammatory state induced by G-CSF injections.

The differential diagnosis of acute cervical pain includes nonvascular and vascular causes such as carotid dissection, carotid occlusion, or vasculitis. In carotid occlusion, rare cause of multiple paraganglioma of carotid is to be ruled out.[4]

Recent guidelines were established by the Society for Vascular Surgery for management of extracranial cerebrovascular disease. These guidelines concern management of carotid stenosis in stroke prevention, and indication of invasive technique should consider neurological symptoms, degree of carotid stenosis, medical comorbidities, and vascular and morphological features.[5] Risk–benefit assessment of carotid invasive procedure must be taken into account as stroke, hemorrhage, infection, cranial nerve injury, and pseudo-aneurysm formation are perioperative complications.[6] In our case, cytopunction was performed to rule out infectious arteritis in our immunocompromised patient.

To our knowledge, only one study has reported histological findings with vascular and fibroblast proliferation and predominantly lymphocytic low-grade chronic active inflammation in TIPIC syndrome.[7]

Differential diagnoses such as Horton's disease, Takayasu's or myelodysplastic aortitis were eliminated due to the acute onset a few days after the G-CSF injection; atypical halo isoechoic at the ultrasound; and the clinical, biological, and imaging improvement spontaneously. In case of doubt between diagnoses, histology may be helpful as the presence of a multinucleated giant cell is pathognomonic of Horton's disease.

Our patient had perivascular infiltration of the carotid, of the carotid bifurcation extending to the aortic arch and the anterior wall of the aorta. Perivascular infiltration was of 4 mm at the carotid bifurcation with no hemodynamic change in color duplex Doppler, similarly to Lercler's series. The extension to the aorta was not described in the series of Leclerc et al., nor in the series of Micieli et al. We can extrapolate that due to the massive recruitment of inflammatory cells, inflammation extends from the carotid to the aorta.

Aspirin may be discussed as a soft plaque may be associated with TIPIC syndrome, and patients can have concomitant neurological transient symptoms.[1] While in some studies, patients are treated with steroids, aspirin, or non-steroidal anti-inflammatory drugs (NSAID)[3]; our patient did not receive therapy (steroids or NSAID) because symptoms evolved favorably without specific treatment and aspirin could not be prescribed due to chemotherapy-induced thrombocytopenia.

In conclusion, we report the first case of G-CSF-induced TIPIC syndrome with a favorable outcome. Transient perivascular inflammation of the carotid artery syndrome is extremely rare. In this particular case, immunosuppressive therapy would have been at high risk of infection given the underlying neutropenia.

AUTHOR CONTRIBUTIONS

Berangere Arnould: Writing – original draft. **Sebastien Miranda:** Supervision; validation; writing – review and editing. **Francois Mignon:** Resources; visualization. **Vincent Camus:** Writing – review and editing.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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