G-CSF induced TIPIC syndrom and large vessel vasculitis a case report

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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 ie Takayasu disease, 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 nonvascular diagnosis with imaging and improvement within 14 days either spontaneously or with anti-inflammatory treatment (1). 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 (Micieli E et al. Transient perivascular inflammation of the carotid artery (TIPIC) syndrome; Vasa 2022). However, TIPIC pathophysiology and triggers remain poorly understood.

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

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 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 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 500mg on February 05, 2022. She already received oral amoxicillin 1g 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/mm3) without fever and was treated with granulocyte colony-stimulating factor (NIVASTIM) for four days.

Before those events, last injection of AZACYTIDINE was performed on January 18, 2022 and 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 16^{th} 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 A). A computed tomography (CT) scan performed the same day revealed tissue infiltration thickening surrounding the left internal carotid artery, the carotid bifurcation, the common carotid artery; as well circumferential thickening of the aortic arch (FIGURE B). 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 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 his left carotid but had no vascular bruit. Other hypothesis was a large vessel vasculitis associated to MDS, Temporal arteries were normal, 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 to the origins of the internal and external carotid arteries (figure C). There were no inflammatory halos of the temporal arteries. 18-FDG-TEP scanner showed hypermetabolism of the left carotid, circumferential hypermetabolism of the aortic arch, 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 were normal. Serum complement C3 and C4 normal.

Inflammatory syndrome decreased as well as neck tenderness. It was decided to not introduce steroids due to spontaneous evolution. Broad spectrum antibiotics were stopped after five days. Ultrasound control 7 days later showed diminished thickening infiltration. 1 month and half later (45 days later) in April 2022 : CT scanner (FIGURE D) 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 nor venetoclax and filgrastim. After 6 months of follow-up, she remains free from disease progression with persistent asymptomatic moderate bicytopenia (neutrophils 1200/mm3, platelets 40 000/mm3).

Discussion

We report a case of TIPIC syndrome induced by G-CSF injection. TIPIC 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.

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 diagnostic 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) and exclusion of different vascular or non vascular entities based on imaging findings (3) and improvement of clinical and imaging findings within two weeks spontaneous or with the use of anti-inflammatory medication (4). Our patient met the four criterias.

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 will 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. 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.

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 and imaging improvement spontaneously.

Our patient had perivascular infiltration of the carotid, extending to the aortic arch and the anterior wall of the aorta. The extension to the aorta wasn't described in the series of Leclerc and al. neither 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.

While in some studies, patients are treated with steroids, aspirin or NSAID (5); our patient didn't receive therapy because symptoms evolved favorably without specific treatment.

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

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FIGURE_A_symptoms_timeline (1).doc available at https://authorea.com/users/622161/articles/645395-g-csf-induced-tipic-syndrom-and-large-vessel-vasculitis-a-case-report

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FIGURE_B (1).doc available at https://authorea.com/users/622161/articles/645395-g-csf-induced-tipic-syndrom-and-large-vessel-vasculitis-a-case-report

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