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PEGFILGRASTIM INDUCED AORTITIS IN A BREAST CANCER PATIENT

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Abstract: Background: Aortitis is a term used to describe a group of clinical conditions characterized by inflammatory disorders limited to the aortic wall. It can be classified into infectious and non-infectious causes. Among the non-infectious causes, rheumatological diseases stand out. Other rare etiologies include adverse drug reactions, such as granulocyte colony-stimulating factors (G-CSF). The association is described in 0.3%-0.47% of cases, but with variations in relation to clinical manifestations and therapeutic approach. **Case presentation**: A 59-year-old woman patient with breast cancer undergoing neoadjuvant chemotherapy with Paclitaxel, Doxorubicin and Cyclophosphamide, associated with Pegfilgrastim (G-CSF) who developed fever, low back pain and dysuria 6 days after taking the medication. Admitted to the hospital on the 5th day of symptoms with nonspecific symptoms and increased inflammatory levels on blood tests and presenting with inflammatory signs in the lower third of the descending thoracic aorta. She carried out etiological investigation, negative for autoimmune and infectious diseases, observed chronological association with the use of medication. Treatment with high dose prednisone was instituted for extended period and Pegfilgrastim was withdrawn in the following chemotherapy cycles. The patient showed clinical and radiological improvement with the instituted therapy. **Conclusions:** Aortitis is a difficult diagnose condition due to nonspecific manifestations and may be associated with different etiologies. It should be considered in patients undergoing chemotherapy using G-CSF, requiring a high degree of suspicion with prompt withdrawal of G-CSF and therapy instituted.

Keywords: Aortitis, Pegfilgrastim, Breast cancer, Granulocyte-colony stimulating factor, Drug-induced aortitis

BACKGROUND

Aortitis is a term used to describe a group of clinical conditions characterized by inflammatory disorders in one or more layers of the aorta (SHARMA et al., 2020). It clinically presents in a variable and non-specific manner, with symptoms including fever, constitutional symptoms, fatigue, malaise and signs of ischemia that vary according to the segment involved: transient ischemic attack (TIA), stroke, angina pectoris, acute myocardial infarction (MI), among others (SHCHETYNSKA-MARINOVA et al., 2021).

The incidence in general population is little known, estimated at 1 – 3 new cases per million year in the population of the United States of America (USA) and Europe (BOSSONE et al., 2016). It can be classified into infectious and non-infectious causes. Among the organisms in infectious aortitis, the most common are Salmonella spp., Staphylococcus spp. and Streptococcus spp., and may also occur in association with Mycobacterium tuberculosis, Treponema pallidum, other gram-negative bacteria and fungi (particularly Candida and Aspergillus) (FOOTE et al., 2005). Among the non-infectious causes, giant cell arteritis (GCA) and Takayasu arteritis (TA) stand out (SHARMA et al., 2020). Other rarer causes include some drugs, such as ergot alkaloids, drugs with dopaminergic effect (HARTLAGE et al., 2014) and there some reports with the use of granulocyte colony-stimulating factor (G-CSF) (LEE et al., 2020).

Granulocyte colony stimulating factors are a group of proteins that regulate hematopoiesis. G-CSF promotes the formation and growth of granulocytes, with more than 90% constituted by neutrophils (TABBARA, 1993). They are recommended as primary or secondary prophylaxis and, in some cases, can be considered as a therapy for neutropenia in adults with cancer (SMITH et al., 2015).

Different forms of Recombinant G-CSFs are available, Filgrastim and Lenograstim, with similar structure and short half-life, and Pegfilgrastim, a pegylated form of Filgrastim, with longer half-life (MOLINEUX, 2011). Adverse effects are generally mild, bone pain being the most common (D'SOUZA et al., 2008). More serious effects, however, such as aortitis have been reported in 0.3%-0.47% of patients (LEE et al., 2020; OSHIMA et al., 2019). It generally occurs in females, in patients over 50 years (LARDIERI et al., 2018; LEE et al., 2020; OSHIMA et al., 2019). Clinical presentation It is also non-specific, making the diagnosis difficult, and is generally carried out based on manifestations and imaging exams showing inflammation in the aortic segment.

We report a case of a patient with breast cancer, undergoing neoadjuvant chemotherapy, who developed aortitis after receiving Pegfilgrastim.

METHODS

The case was reported at Hospital São Rafael, a reference hospital in Salvador city in the state of Bahia, using data extracted from the electronic medical record. A literature review was also carried out, including clinical and epidemiological aspects, as well as diagnosis and treatment.

Non-systematic literature review occurred through research in PubMed database, until January 22, 2023, using the keywords "aortitis" and "granulocyte colony-stimulating factor", in addition to get articles and guidelines. There was no language restriction and the selection of articles was based on relevance to the topics covered in this review, such as epidemiology, etiology, clinical characteristics, diagnosis and treatment.

The study was submitted and approved by the Research Ethics Committee of Hospital São Rafael on 03/07/2023, CAAE 67351123.8.0000.0048, following the ethical precepts of resolution 466/2012 of the Conselho Nacional de Saúde. The patient had her confidentiality assured and only participated in the study after reading and signing the informed consent, giving permission to publication of the case.

The study presents no conflicts of interest.

CASE REPORT

A 59 year old woman patient, 59 years old, with a medical history of asthma, cholecystectomy and hysterectomy with oophorectomy, undergoing treatment for breast cancer (invasive ductal carcinoma, cT2cN3M0, Nottingam grade 2, RE + 90%, PR + 70, Ki67 50%, luminal B) in right breast with neoadjuvant chemotherapy, having performed 12 sessions with Paclitaxel and 1 session with Doxorubicin 105.6mg and Cyclophosphamide 1056mg associated with Pegfilgrastim (G-CSF) 6mg (didn't use Pegfilgrastim previously), last session carried out 11 days before hospital admission. Admitted to the hospital with dysuria, fever and low back pain, on the 5th day of symptoms. She denied weight loss. On physical examination, she presented with a BP: 114 x 55 mmHg, HR: 107 bpm, T°: 37.7 °C, RR: 21 ipm, SatO2: 98%, weight: 70 kg, without changes in the respiratory and cardiovascular segments, with a port-a-cath catheter on left hemithorax, on abdominal examination with mild pain on palpation of hypogastrium, negative Giordano's sign, and on vascular examination with palpable and symmetrical carotid pulses, palpable and symmetrical temporal arteries, painless, without thickening, peripheral pulses palpable and symmetrical. Laboratory tests were carried out with evidence of a significant increase in inflammatory tests (CRP: 257.6 mg/dL, ESR: 120 mm/h) and leukocytes (18,850/µL with 80% segmented and 5% band), without elevation of procalcitonin (Procalcitonin: 0.205 ng/mL), without

changes in renal function (Urea: 28 mg/dL and Creatinine: 0.65 mg/dL), without significant hydroelectrolyte disturbances (Na: 134 mEq/L and K: 4, 7 mEq/L) and urinalysis without signs of infection. Imaging exams were done, chest computed tomography and abdominal tomography with contrast, revealing parietal thickening in the lower third of the descending thoracic aorta, circumferential, measuring up to 0.6 cm in thickness and for an extension of approximately 10.6 cm in the longitudinal axis, without promoting stenosis (Figure 1). There were no inflammatory signs on abdominal aorta segment, with mild diffuse parietal thickening in bladder. The patient had a non-contrast chest CT scan 46 days prior to the current examination with no evidence of an inflammatory process in the entire segment of the aorta evaluated (Figure 2).

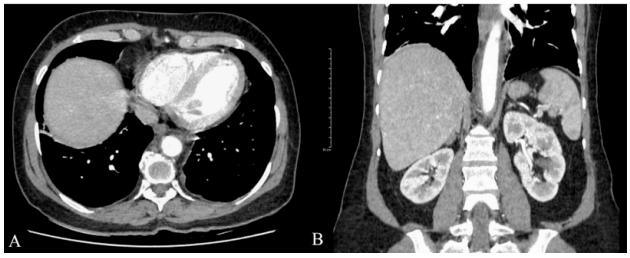

Figure 1 Contrast-enhanced CT scan of the chest and abdomen performed upon hospital admission showing evidence of parietal thickening in the lower third of the descending thoracic aorta, circumferential, measuring up to 0.6 cm in thickness and for an extension of approximately 10.6 cm along the longitudinal axis. A. Axial section. B. Coronal section.

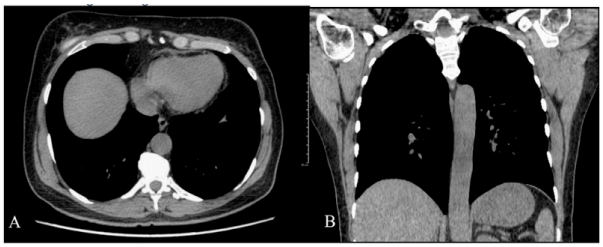

Figure 2 A non-contrast-enhanced chest CT scan 46 days before hospital admission showed vascular structures with preserved diameter without signs of inflammation. A. Axial sction. B. Coronal section.

In etiological investigation, non-reactive FTA-ABS and VDRL, non-reactive anti-HCV, non-reactive anti-HBc and HBsAg with reactive anti-HBs, negative HIV 1 and 2 antibodies test, negative IGRA measurement, non-reactive ANA , non-reactive ANCA (p-ANCA and c-ANCA) and IgG4 subclass measurement of 668 (reference value: 30-2010). Peripheral blood cultures, port-a-cath removal with catheter tip culture and urine cultures were also requested. Initially antibiotic therapy with Meropenem was started, with fever, low back pain and elevated inflammatory tests (CRP: 322 mg/dL) and leukocytes (16,950/μL with 80% segmented, without deviation) persisting. Associated Daptomycin on the 6th day of hospitalization to cover gram-positive germs, when she had the last febrile episode, and Prednisone 60mg/day on 7th day. The other clinical symptoms improved on the 9th day of hospitalization (14 days after the onset of symptoms), pending culture results were negative and there was a drop in inflammatory tests (CRP: 82 mg/dL on the 13th day > 25 mg/dL at hospital discharge) and leukocytes (13,930/μL on the 13th day, with a drop to 12,420/μL at hospital discharge). She was discharged from hospital on the 16th day, having completed the use of Meropenem for 16 days, Daptomycin for 10 days and Prednisone 60mg/day for 9 days, which was continued after discharge.

Performed consecutive chemotherapy sessions without using of Pegfilgrastim and proceed outpatient follow-up with a rheumatologist, with the use of Prednisone 60 mg/day continued for another 26 days, tapering off in the subsequent 175 days (total time of Prednisone use of 210 days). She presented complete resolution of clinical symptoms, without recurrence, and a drop in inflammatory tests. A new imaging examination was done 255 days after the onset of symptoms demonstrating a reduction in concentric parietal thickening, previously with a maximum thickness of 0.6cm, to 0.3cm (Figure 3).

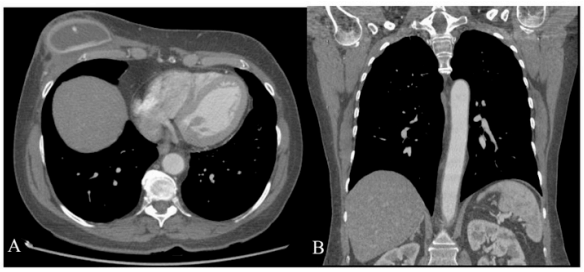

Figure 3 CT of the chest with contrast 255 days after the onset of symptoms, demonstrating a reduction in the concentric parietal thickening of the aortic segments (more evident at the level of the arch, with a slight extension to the emergence of the supra-aortic branches, and in the descending portion), with parietal thickness maximum of 0.3 cm (previously 0.6 cm). A. Axial section. B. Coronal section.

DISCUSSION

This report described a case of a patient with breast cancer who developed aortitis. The main suspicion was aortitis associated with Pegfilgrastim, since there was a strong association between the disease and the medication and the patient had a recent normal chest tomography. There are no specific laboratory markers for the diagnosis of aortitis, normally presenting with non-specific elevation of inflammatory markers (CRP and ESR) in most patients. Some new, more specific markers for arterial inflammation are still being studied, such as pentraxin 3 (PTX3) (BENHURI et al., 2020). Other tests can be used in the appropriate clinical context, such as antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) and rheumatoid factor (RF). In case of infectious aortitis, microbiology is important for identifying the etiological agent. Skin tests for tuberculosis and serology for syphilis are reserved for when there is clinical suspicion (GORNIK; CREAGER, 2008). Imaging tests also help in identifying and locating acute and chronic changes in the aorta, due to inflammation, edema and fibrosis and in characterizing luminal changes as well as associated complications. The modalities include vascular ultrasound and echocardiography, computed tomography (CT) and computed tomography angiography (CT angiography), magnetic resonance imaging (MRI) and magnetic resonance angiography (MR angiography), positron emission tomography (PET) and angiography (BOSSONE et al., 2016). In the case reported blood cultures were requested to rule out infectious etiology and rheumatological autoantibodies, serology and IgG4 measurement were requested to rule out other underlying diseases. Furthermore, the patient did not present other associated symptoms that could suggest another etiology, such as arthritis, oral ulcers, headache and amaurosis fugax. It is noteworthy that although blood cultures are positive in 50-85% of cases of acute bacterial aortitis (SHCHETYNSKA-MARINOVA et al., 2021), the patient showed clinical improvement with antibiotic time considerably shorter than that recommended in the literature, 16 days of Meropenem and 10 days of Daptomycin in this case, with recommended being use for 6 weeks to 6 months, which can be maintained throughout

life in some cases. In addition, she didn't have undergone surgery repair, recommended in all cases of infectious aortitis, and have not developed common associated complications. The radiological diagnosis was performed with chest CT angiography and compared with a previous chest CT, a method considered good for visualizing mural thickening and periaortic inflammation and changes in adjacent tissues, in addition to providing excellent visualization of the vessels, easily distinguishing mural and luminal anatomy (HARTLAGE et al., 2014).

Aortitis has been reported as an adverse effect in patients using different G-CSF formulas, although Pegfilgrastim has been the most associated, associated with different neoplasms (breast, lung, colon, prostate, lymphoma, ovarian, uterine, esophagus) and chemotherapy regimens, showing a causal relationship with G-CSF regardless of the tumor or chemotherapy used (LARDIERI et al., 2018; LEE et al., 2020; OSHIMA et al., 2019).

The time of clinical manifestation in this report was 6 days after taking the medication, which although varies in the literature, a similar chronology is found. Presentation time is reported from 0-180 days after taking the medication, an average of 12.3 days, in cases presenting 12-17 days after or 6 – 15 days, with an isolated case occurring after 365 days. The lesion was located in the lower third of the descending thoracic aorta. On literature the most common location is described as the thoracic aorta, but there are also cases in which the thoraco-abdominal and abdominal portions are affected (LARDIERI et al., 2018; LEE et al., 2020; OSHIMA et al., 2019).

Treatment and treatment time are not well defined, and are generally done with glucocorticoids, based on the treatment of other large vessel vasculitis (HELLMICH et al., 2020), in addition to not using Pegfilgrastim in subsequent chemotherapy cycles, since the reintroduction of the drug is associated with reactivation of the disease (LARDIERI et al., 2018; LEE et al., 2020). In the case in question, glucocorticoid (Prednisone) was also used for a prolonged period of time (total of 210 days) and Pegfilgrastim was avoided again, but the improvement cannot be clearly attributed to the Prednisone, since the patient began to show clinical improvement before the introduction of the medication, characterized as the last febrile episode on the 6th day of hospitalization (11 days after onset of symptoms), presenting complete clinical resolution and a decrease in inflammatory parameters subsequently. Control imaging exams performed at a later time (after 255 days) confirmed partial improvement of the lesion. In a series of cases, resolution was reported within a period of 11 days to 15 months (LARDIERI et al., 2018) and in a review with 48 cases, it is highlighted that the group that did not used steroids, composed of 19 patients, presented remission in 4 – 32 days, average of 15.7 days, in contrast to 29 patients in the group that used corticosteroids, 6 – 82 days, average of 16 days, with no statistical significance (HOSHINA; TAKEI, 2021).

CONCLUSION

Aortitis is a condition that is difficult to diagnose due to non-specific manifestations and can be associated with different etiologies with serious associated complications. After the most common conditions have been ruled out, it should be considered in chemotherapy patients using G-CSF, requiring a high degree of suspicion to promptly discontinue the medication in subsequent cycles and initiate therapy, which, although not established, is generally performed with glucocorticoids.

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