Carotidynia after anticancer chemotherapy

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ABSTRACT Carotidynia is characterised by inflammation limited to the common carotid artery, which has been recognised as a distinct disease entity by advanced vascular imaging. Although most cases of carotidynia are idiopathic, we herein present a case of carotidynia after anticancer chemotherapy. A 64-year-old male patient received docetaxel followed by granulocyte-colony stimulating factor (G-CSF) for the treatment of lung squamous carcinoma. After the treatment, bilateral cervical pain developed. Vascular imaging, including magnetic resonance imaging, computed tomography and ultrasonography, showed characteristics specific for carotidynia. Although there was no strong confirmation using tests such as a challenge test, our observations suggest that docetaxel or G-CSF could be a causative drug triggering carotidynia.

Keywords: adverse drug reactions, carotidynia, docetaxel, granulocyte-colony stimulating factor

INTRODUCTION

Carotidynia was first described by Fay in 1927 as an atypical facial neuralgia characterised by tenderness on the carotid artery around the bifurcation. After further investigation by Roseman in 1967, carotidynia was widely accepted as a distinct disease entity. In 1988, the International Headache Society (IHS) classified carotidynia as a headache associated with vascular disorders. IHS indicated the following diagnostic criteria for carotidynia: (a) neck pain, which may radiate to the head; (b) tenderness, swelling, or increased pulsations overlying the carotid artery; (c) the absence of structural abnormalities; and (d) self-resolution of the syndrome within two weeks. However, in the 1990s, these clinical-based criteria were re-evaluated, and carotidynia was reclassified as a nonspecific syndrome characterised by unilateral or bilateral neck pain resulting from nonvascular causes. Thus, the second edition of the IHS classifications did not include carotidynia.

In the last decade, carotidynia was recognised as a distinct entity because data from advanced imaging techniques for carotid vascular disease, including magnetic resonance (MR) imaging, computed tomography (CT), and ultrasonography, revealed images with features specific for carotidynia. These images showed characteristics of a thickened carotid sheath localised to the symptomatic carotid artery, while the luminal wall and blood flow were observed to be normal.

To date, neither the aetiology nor the pathology of carotidynia has been well documented. Thus, in many cases, the onset of the syndrome has been classified as spontaneous. However, a few reports have suggested that some medications can cause carotidynia. Herein, we describe a case of carotidynia that occurred after anticancer chemotherapy. Although there is no definitive evidence, our findings suggest that docetaxel or granulocyte-colony stimulating factor (G-CSF) may cause carotidynia.

CASE REPORT

A 64-year-old man presented with bilateral cervical pain, accompanied by severe tenderness on pressure and a high fever of 39.4°C. He had previously received chemotherapy for stage IV lung squamous cell carcinoma accompanied by brain metastasis. The lung tumour was located in the distal right upper lobe, and no invasion into the aorta or superior vena cava was noted. The patient received six cycles of combined chemotherapy comprising carboplatin and pemetrexed, followed by two cycles of single-dose pemetrexed. We altered this regimen because of progressive disease for the last cycle, and administered docetaxel at a dose of 60 mg/m² body surface area as second-line chemotherapy. To prevent an allergic reaction, 9.9 mg of dexamethasone was administered immediately before the second-line chemotherapy. Ten days after docetaxel administration, we administered 75 mg of filgrastim, a recombinant G-CSF, via daily subcutaneous injection for three days because the patient’s white blood cell (WBC) count had decreased to 1,200/µl, with a neutrophil count of 340/µl, although no infection was detected. G-CSF was not used in the previous chemotherapy.

Five days after initiation of G-CSF and 15 days after docetaxel administration, the patient suddenly experienced pulsation and tenderness in his neck along the length of the common carotid artery distal to the bifurcation. Positional radiating pain was absent. Slight swelling around the bifurcation was observed, but no carotid bruit was audible. At that time, the patient’s WBC and neutrophil counts were 24,700/µl and 19,500/µl, respectively, with a C-reactive protein concentration of 11.24 mg/dL. Other blood examination parameters were unremarkable.

MR imaging detected T1-enhanced tissue with gadolinium enhancement of the thickened carotid sheath (Fig. 1a). We used only acetaminophen, a nonsteroidal anti-inflammatory drug, because carotidynia is a benign disease that often remits spontaneously. We planned to use a steroid only if the patient’s symptoms worsened. His symptoms disappeared without steroid therapy eight days from onset. We confirmed resolution of the discriminative findings on

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MR imaging (Fig. 1b). Additionally, CT (Fig. 2) and ultrasonographic findings (Fig. 3) suggested self-resolution of carotidynia, too. It is worth noting that minimal narrowing of the lumen (Fig. 2b), when compared against CT images obtained after resolution (Fig. 2c), was observed at onset. Neither dissection nor thrombus of the inner vessel was detected in these images.

Although cancer patients frequently suffer from bacterial infection, often as a consequence of neutropenia associated with anticancer chemotherapy, no infectious focus was detected in our patient. Blood and serological examinations showed no evidence of cytomegalovirus or Epstein-Barr virus infection. While we had suspected temporal arteritis (i.e. giant cell arteritis) because his symptoms were symmetrical and located along an artery, we found no ischaemic changes in the optic disc and no typical symptoms of temporal arteritis. Overall, these diagnostic indications in our patient are in line with those previously described in other case reports of carotidynia.

We subsequently planned another round of chemotherapy using non-taxane derivatives without G-CSF administration, followed by initiation of daily oral administration of TS-1 – a combination drug of tegafur, gimeracil and oteracil potassium – as third-line chemotherapy. Neither carotidynia nor vasculitis was detected during the administration of TS-1, and the patient was still alive two months from the onset of carotidynia.

**DISCUSSION**

Even though the definition of carotidynia is controversial, many case reports have suggested carotidynia to be an idiopathic vasculitis limited to the distal common carotid artery. Our patient presented with symmetrical neck pain, accompanied by tenderness, swelling, and increased pulsations overlying the carotid artery. However, these symptoms resolved after a week, without steroid therapy. The clinical course of our case met the old criteria for carotidynia. In addition, the diagnostic images of the carotid artery in our patient were found to be congruent with recent reports of carotidynia indications, such as thickened rim enhancement observed on postgadolinium T1-weighted MR imaging and hypoechoic thickening of the aortic wall on ultrasonography. Thickening of the aortic wall was limited to the common carotid artery distal to the bifurcation, and was not accompanied by the presence of a thrombus or structural abnormalities.
Although statistically supported conclusions cannot be drawn due to a lack of analysis of carotidynia cases, most case reports describe similar characteristics. In our patient, the clinical and imaging indications supported the diagnosis of carotidynia. The onset of symptoms in our patient occurred immediately after anticancer chemotherapy, strongly suggesting an association between carotidynia and medications, especially docetaxel or G-CSF. Despite unknown aetiology, a few recurrent cases of carotidynia have been reported.\(^9,10,13\) One recurrent case associated with the repeated administration of a selective serotonin reuptake inhibitor strongly suggests that some medications can trigger carotidynia.\(^11\) However, as it is difficult to define a direct relationship between carotidynia and medications, adverse drug reactions (ADRs) should be diagnosed with caution. In our patient, the ADR probability scale\(^12,13\) suggested a probable ADR with docetaxel or G-CSF. We could not exclude in our patient an ADR to either docetaxel or G-CSF because the drugs were administered just before the onset of carotidynia.

A few previous reports have reported the use of docetaxel in cases of carotidynia.\(^9,10,13\) In a case of carotidynia presenting after chemotherapy for pancreatic cancer, gemcitabine was assumed to be the drug responsible for carotidynia, although docetaxel was used simultaneously.\(^9\) In a case of large vessel vasculitis that included not only the carotid artery but also the aorta, suggesting the occurrence of carotidynia, the patient’s symptoms presented after anticancer chemotherapy with gemcitabine, which was assumed to be the drug responsible for carotidynia, even though docetaxel was also concurrently administered.\(^13\) The reason why gemcitabine was determined as the drug responsible for carotidynia in these reports\(^9,13\) was because gemcitabine-associated vasculitis has been well documented.\(^14\) However, these gemcitabine-associated vasculitis cases\(^9,13\) showed necrotising inflammation of the vessel wall accompanied by endothelial thrombosis, which is in conflict with proliferative inflammation without thrombosis in a case of pathologically confirmed carotidynia.\(^15\)

In another case of carotidynia following anticancer chemotherapy, docetaxel, carboplatin and trastuzumab, but not gemcitabine, were administered.\(^10\) Because challenge tests using the candidate drugs were not conducted in these case reports,\(^9,10,13\) it is difficult to determine whether these cases were ADRs, and if so, the drug responsible for carotidynia. In addition, the mechanism by which docetaxel causes vasculitis is controversial, and no cases of docetaxel-induced vasculitis in the large artery have been reported. However, these case reports\(^9,10,13\) as well as our present case, support the possibility that an ADR to docetaxel causes vasculitis, including carotidynia. A case of carotidynia arising in the presence of concurrent chemotherapy for acute lymphocytic leukaemia (ALL) has also been reported.\(^23\) However, the types of anticancer drugs used, and whether G-CSF (which is frequently used during anti-ALL chemotherapy) was administered were not documented.\(^24\)

G-CSF has been widely used for recovery from neutropenia after anticancer chemotherapy, and neutrophil recruitment is a possible causative mechanism for vascular inflammation, with a case of abdominal aortitis caused by G-CSF having been reported.\(^16\) In addition, a case in which carotidynia was histologically confirmed showed lymphocytic inflammation with fibrosis, although the recruitment of neutrophils was also observed.\(^11\) In our patient, blood neutrophil count was 19,500/µL at the onset of carotidynia. Although this neutrophycytosis could be a result of nonspecific inflammation resulting from carotiddynia, we speculated that G-CSF could be a cause.

In the present case, neither docetaxel nor G-CSF could be determined as a causative agent of carotidynia because these drugs did not fulfil the criteria for ADR. In addition, the mechanism by which these drugs cause vasculitis remains controversial. However, we opine that docetaxel or G-CSF could cause carotidynia. Although carotidynia is very rare and mostly idiopathic, we emphasise the importance that carotidynia be considered when a patient presents with anterior neck pain after anticancer chemotherapy.

REFERENCES