

## CONCISE REPORT

# Obstruction of the pulmonary artery by granulomatous vasculitis: a clinical, morphological, and immunological analysis

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The case of a 45 year old woman presenting with fever of unknown origin, headache, polyarthralgia, and chest pain is described. Computed tomography scans and angiography disclosed a mediastinal tumour with a complete obstruction of the right pulmonary artery, positron emission tomography scans showed a tracer accumulation in the walls of the pulmonary artery and the aorta. Thoracotomy was performed and subsequent histological analysis of multiple biopsy specimens led to the diagnosis of a form of giant cell arteritis of the pulmonary artery. Immunological analysis of the cytokine profile of peripheral blood mononuclear cells (PBMC) showed a markedly increased production of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) and interleukin 2 (IL2) and a normalisation of TNF $\alpha$  production after successful treatment. In contrast, the production of interferon  $\gamma$ , IL4, IL6, IL10, and IL13 was normal. Furthermore, an expanded subset of double positive CD4+/CD8+ T cells was remarkable, as well as an increased expression of the IL2 receptor on PBMC. Immunomodulatory treatment with steroids and methotrexate was started and led to a rapid resolution of symptoms and morphological changes. The right pulmonary artery, however, remained occluded. The particular features of this case are reviewed with consideration of its clinical, diagnostic, histopathological, and immunological characteristics and are compared with other reported findings.

### CASE REPORT

We here report on a 45 year old white woman who was admitted to our department of infectious diseases in January 2001. The clinical symptoms described by the patient consisted of intermittent episodes of fever up to 39°C, polyarthralgia, headache, and chest pain, which predominated during inspiration. Several flare ups of symptoms had been reported during the past 12 months, the last one beginning three weeks before admission.

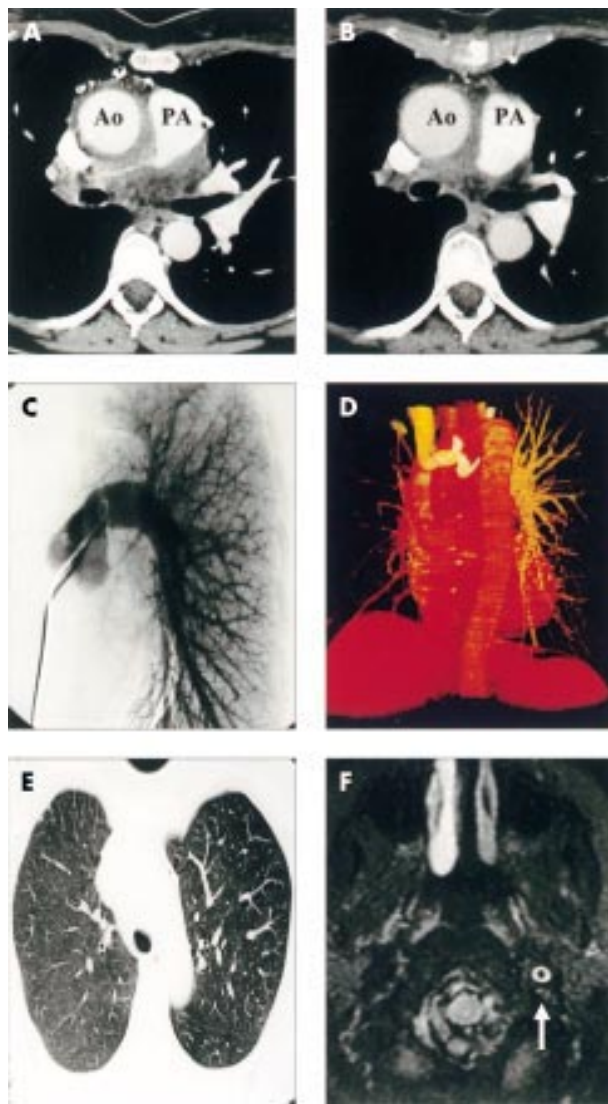
The patient's medical history was fairly uneventful, showing only one episode of hepatitis A infection as well as an appendectomy several years ago. The only uncommon feature was a symmetrical uveitis, which had a history of five years recurring up to three times a month. Despite repeated medical examinations by ophthalmologists its cause remained unclear. However, the symptoms responded well to local steroid treatment. Otherwise, the patient felt healthy, exercise was well tolerated, and the patient did not smoke or drink alcohol. No continuous drug treatment was reported, although non-steroidal anti-inflammatory drugs were used on demand for the symptoms described above and provided good relief.

Physical examination showed a bilateral conjunctival infection, but was otherwise normal. In particular, no clinical signs of an infection of the upper or lower respiratory tract were present, which had been initially suspected because of fever and chest pain. Electrocardiography as well as a chest x ray

examination were performed and yielded normal results. Based on the clinical symptoms of the patient with fever, chest pain, and arthralgia, several disease entities such as infection, autoimmune disease (such as systemic lupus erythematosus), and neoplasm had to be considered and led to a more complete diagnostic procedure. A multislice computed tomographic (CT) scan of the chest was performed, which disclosed a mediastinal tumour localised proximate to the aortic arch and the pulmonary arteries (figs 1A and B). Most importantly, the right pulmonary artery appeared infiltrated and obstructed by this lesion. This image was confirmed by conventional angiography, showing a complete obstruction of the main right pulmonary artery (fig 1C). As a consequence of this obstruction, an asymmetrical perfusion of the lungs was evident from angiography, showing hypoperfusion of the right lung and hyperperfused and dilated pulmonary vessels in the left lung (figs 1D and E). Cerebral perfusion was also analysed by single photon emission tomography and magnetic resonance (MR) angiography, which disclosed a normal and symmetrical cerebral perfusion. However, MR imaging also showed a non-obstructive thickening of the wall of the right carotid artery, which was not found at the contralateral side (fig 1F). Positron emission tomography (fluorodeoxyglucose-PET) disclosed an accumulation of tracer in the aortic arch and the pulmonary arteries colocalising with the lesion found in the CT scan (web extra figure W1).

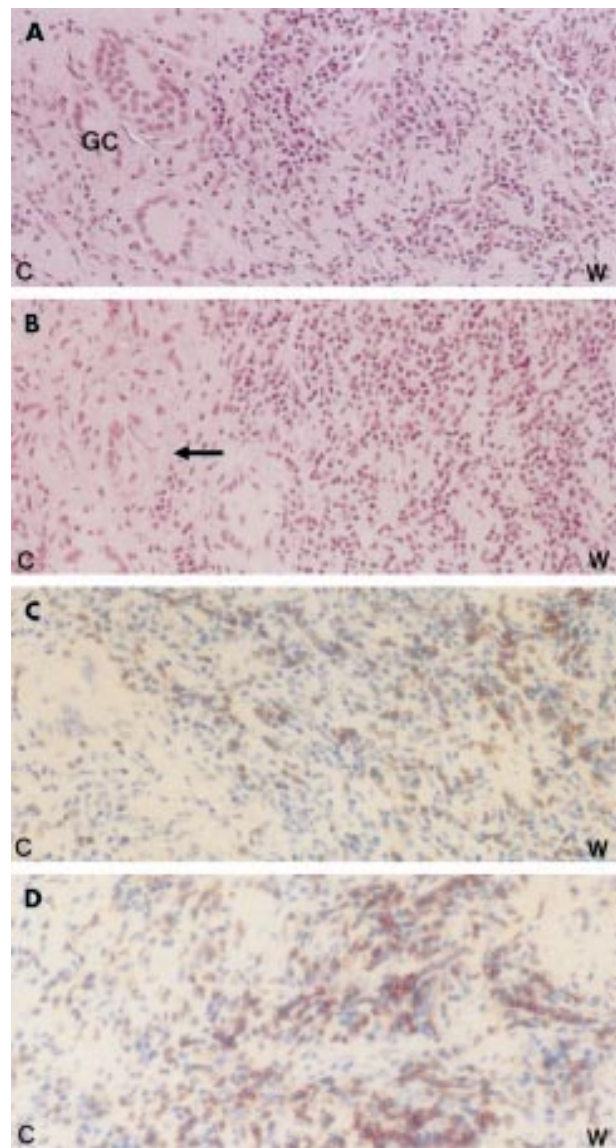
Laboratory examination showed an increase of acute phase parameters, the C reactive protein was 156 mg/l (normal up to 5 mg/l) and the erythrocyte sedimentation rate was 70 mm/1st h (normal up to 10 mm/1st h). Parameters of kidney, liver, and thyroid function were normal. Blood counts showed a moderate anaemia (haemoglobin 102 g/l), with microcytosis and hypochromatosis as well as mild thrombocytosis ( $399 \times 10^9/l$ ), but normal leucocyte counts ( $7.1 \times 10^9/l$ ). Differential blood count disclosed absolute and relative lymphopenia ( $0.7 \times 10^9/l$ ). Testing for rheumatoid factors, antinuclear antibodies, and antibodies to dsDNA was negative. The assessment for cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA; immunofluorescence and anti-myeloperoxidase enzyme linked immunosorbent assay (ELISA)) and perinuclear ANCA (p-ANCA; immunofluorescence and anti-proteinase 3 ELISA) was negative. Also, the levels of total serum protein,  $\gamma$  globulins, and IgG, IgA, and IgM were within normal ranges.

**Abbreviations:** ACR, American College of Rheumatology; ANCA, antineutrophil cytoplasmic antibodies; CT, computed tomography; ELISA, enzyme linked immunosorbent assay; GCA, giant cell arteritis; IL, interleukin; MR, magnetic resonance; PBMCs, peripheral blood mononuclear cells; PET, positron emission tomography; TA, Takayasu arteritis; TNF, tumour necrosis factor



**Figure 1** Imaging: CT scan, conventional and MR angiography CT scans were performed before starting the immunosuppressive treatment (A) and after two months of treatment (B). An axial thoracic section shows a diffusely infiltrating mass surrounding the aorta and the pulmonary artery. After successful treatment a marked reduction of pathological tissue is evident. Angiography of the pulmonary arteries shows blockage at the origin of the right main pulmonary artery, indicating a complete occlusion of this vessel (C). This is also evident in a three dimensional reconstruction of the heart and the large vessel (D). As a consequence an asymmetrical perfusion of the lungs with hypoperfusion right and compensatory hyperperfusion at the left side is seen (E). MR angiography (F) showed a normal cerebral perfusion; however, a unilateral thickening of the wall of the right internal carotid artery was detected.

Angiosarcoma of the aorta or pulmonary vessels, or both, was suspected, and thoracotomy was performed. The intra-operative macroscopic aspect was a diffusely spreading tumorous lesion of the mediastinum showing infiltration of the large vessels, especially of the ascending aorta and the pulmonary arteries. The lesion was considered to be inoperable. However, for diagnostic purposes multiple biopsy specimens were taken from the pulmonary artery. Interestingly, the histological analysis did not show any neoplastic transformation but a granulomatous inflammatory disease localised to the media and the adventitia of the pulmonary artery. Inflammatory lesions were formed as granulomas, with a peripheral wall consisting of a dense infiltration of mononuclear cells and surrounding a central area with elastic



**Figure 2** Histology. Microphotographs show haematoxylin and eosin stain (A, B) and immunostain (C, D) of biopsy material. Both the centre (C, left) and the wall (W, right) of an intimal granuloma are shown. (A) Giant cells; (B) giant cell engulfing an elastic fibre (arrow); (C) CD4+; and (D) CD8+ T cell in the wall of the granuloma.

fibres, epithelioid cells, and interspersed giant cells (figs 2A and B). Moreover, both CD4+ and CD8+ T cells were found in these lesions and both subtypes of T cells were localised in the peripheral wall of these granulomas (figs 2C and D). A large number of fragments of elastic fibres were present in these lesions, localising them to the elastic layer of the vessel wall and indicating a destruction of the elastic vessel wall by the inflammatory infiltrate. Indeed, most of the giant cells showed phagocytosed elastic fibres in the cytoplasm (fig 2B).

The patient was diagnosed as having a form of giant cell arteritis (GCA) of large vessels and received systemic treatment with steroids (initially, 250 mg methylprednisolone) and methotrexate (25 mg/week as subcutaneous injection). Only 48 hours after the start of treatment, the conjunctival infection as well as clinical signs of disease disappeared, the acute phase response normalised within three weeks, and a control CT scan performed after two months showed a marked reduction in the size of the mediastinal inflammatory masses. The right pulmonary artery, however, remained obstructed, although the patient remained

**Table 1** Cytokine profile of PBMC before and after treatment. Results are shown as percentages

| Cytokine     | Before treatment |      |           | After treatment |      |           |
|--------------|------------------|------|-----------|-----------------|------|-----------|
|              | CD4+             | CD8+ | CD4-/CD8- | CD4+            | CD8+ | CD4-/CD8- |
| IL2          | 73               | 56   | 10        | 65              | 24   | 5         |
| IL4          | 6                | 1    | 2         | 5               | 1    | 1         |
| IL6          | 0                | 0    | 4         | 0               | 0    | 13        |
| IL10         | 1                | 0    | 1         | 1               | 0    | 1         |
| IL13         | 5                | 1    | 0         | 4               | 0    | 0         |
| TNF $\alpha$ | 69               | 55   | 12        | 29              | 18   | 5         |
| IFN $\gamma$ | 21               | 57   | 26        | 20              | 49   | 11        |

Intracellular cytokine production was analysed in CD4+ and CD8+ T cells as well as in CD4-/CD8- cells (B cells, monocytes) before and after treatment. Note the decrease in TNF $\alpha$  production in CD4+ and CD8+ cells as well as the decrease in IL2 production in the CD8+ subset after successful treatment.

asymptomatic. Steroids could be tapered and finally stopped after three months of treatment, leaving the patient with a maintenance single treatment of methotrexate.

Before the start of treatment an immunological assessment of peripheral blood mononuclear cells (PBMCs) was performed. It included the assessment of lineage-specific surface markers for leucocyte and lymphocyte typing, the assessment of other surface markers for lymphocyte activation, and the analysis of intracellular cytokine production of these cells. Intracellular cytokine production was also assessed after successful treatment of the disease. All analyses were carried out by fluorescence activated cell sorter. Whereas the number of neutrophils ( $5.08 \times 10^9/l$ ) and monocytes ( $0.59 \times 10^9/l$ ) was normal, total lymphocytes ( $0.92 \times 10^9/l$ ) and all lymphocyte subsets (T cells  $0.73 \times 10^9/l$ , CD4+  $0.47 \times 10^9/l$ , CD8+  $0.29 \times 10^9/l$ , B cells  $0.18 \times 10^9/l$ ) were below the normal range. The number of natural killer cells was normal ( $0.14 \times 10^9/l$ ). Five per cent of peripheral lymphocytes were activated, carrying surface HLA-DR. Interestingly, the number of CD4/CD8 double positive cells ( $0.07 \times 10^9/l$ ) was clearly raised in this patient with Takayasu arteritis (TA) compared with healthy subjects (10% of the total lymphocyte count compared with 1% in healthy controls). Two independent laboratories confirmed this result. No significant differences between the patient with TA and healthy subjects were found for the expression of CD11a (LFA-1), CD28, CD45RA (naive T cells), CD45RO (memory T cells), and CD49d (VLA-4). Only the number of CD25 (interleukin 2 (IL2) receptor) positive cells was increased in this patient (45% positive cells) compared with normal subjects (25% positive cells). The analysis of intracellular cytokine production disclosed a highly activated production of tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) and IL2 in both the CD8+ and the CD4+ subsets (table 1). Production of IL4, IL6, IL10, and IL13 was low. Successful treatment markedly decreased TNF $\alpha$  production by CD4+ and CD8+ T cells and reversed it to the level found in healthy subjects (web extra figure W2).

## DISCUSSION

We have described here a form of granulomatous vasculitis with occlusion of the pulmonary artery and subclinical involvement of the aorta and carotid artery. Its clinical presentation as a combination of fever of unknown origin, uveitis, and a mediastinal mass in the CT scan is unusual. In addition, the advanced disease state in the pulmonary circulation with only subclinical involvement of the systemic circulation does not facilitate its diagnosis and classification.

Diagnosis of large vessel vasculitis itself is tricky, because clinical symptoms of disease are usually heterogeneous, a single reliable diagnostic test is lacking, and its prevalence is low. Histological verification of an inflamed vessel wall is a diagnostic paradigm of the diagnosis of vasculitis. Herein, histological analysis disclosed granulomatous infiltration of all layers of the pulmonary artery. These lesions consisted of a

central core with epithelioid and giant cells and a peripheral lymphocellular infiltration. Their presence within large sized vessels indicates either TA or GCA.

Both GCA and TA can affect the pulmonary artery. A concomitant involvement of the pulmonary artery is found in 40–50% of cases of TA<sup>1</sup> and in about 5% of cases of GCA.<sup>3</sup> In addition, rare cases of a primary vasculitis of the pulmonary artery have been reported which were attributed to both types of disease (TA<sup>3–10</sup>; GCA<sup>11–18</sup>). Most of these patients presented with a rather severe course of disease, such as pulmonary thromboembolism, pulmonary hypertension, or severe haemoptysis, leading to surgical interventions such as pneumonectomy. In contrast, the patient presented here had a relatively mild and non-specific clinical course, but a severe and advanced histopathological disease stage. Occlusion of the pulmonary artery must have occurred gradually, probably owing to a narrowing of the lumen by the inflamed vessel wall and not owing to thrombosis.

This case is an example of the dilemma of classification and diagnosis of vasculitis with atypical clinical presentation. If the American College of Rheumatology (ACR) criteria for the diagnosis of TA<sup>19</sup> and GCA<sup>20</sup> are applied this patient fulfils three of five criteria for the diagnosis of GCA (headache, raised erythrocyte sedimentation rate, and positive histology), but none of the six criteria for TA. Even if the positive angiography with pulmonary artery occlusion is counted, only one of six criteria for the diagnosis of TA is fulfilled. Thus, according to the ACR criteria this patient would be diagnosed as GCA with involvement of the pulmonary artery. However, diagnosis and classification seem to be more complex. The ACR criteria for the diagnosis of TA are based on the stenotic phase of TA and therefore signs of arterial stenosis are overrepresented, contributing to four or five of the criteria. In contrast, the ACR criteria for GCA are much more based on clinical features of the disease itself and do not include signs of arterial stenosis. Given the fact that the course of TA also includes a prestenotic phase, the ACR criteria are difficult to apply for TA when clinical signs of arterial stenosis or occlusion are absent. This is also true for this case because the major disease was localised in the pulmonary circulation, whereas pathological changes of the systemic circulation were subclinical.

Beside the ACR criteria, various other clinical features may help to discriminate between TA and GCA. For example, the median age of patients with GCA is 72 years, whereas that of TA is 25 years. Our patient was 45 at the beginning of systemic symptoms and the history of uveitis was even longer. Furthermore, the advanced state of pulmonary artery disease suggests that the onset of disease was considerably earlier in life and thus makes TA the more likely diagnosis. Also, many of the typical clinical symptoms of GCA, such as temporal artery tenderness, polymyalgia, blurred vision, jaw claudication, scalp tenderness, throat and tongue pain, or depression were completely missing. This suggests that even if the ACR criteria

for GCA were fulfilled by this case, it is a very untypical example of GCA. With respect to the diagnosis of TA, typical clinical signs of a stenotic form of TA were lacking, but the involvement of the aorta and one of its branches was at least identified subclinically. This raises the question whether the patient described here had a prestenotic form of TA.

The diagnosis of prestenotic TA is a challenge because early therapeutic intervention is likely to prevent narrowing or even occlusion of the arterial lumen. Whereas conventional angiography can only detect stenosis but not arterial wall thickening, other techniques such as multislice CT scan, MR angiography, and ultrasound may detect early inflammatory thickening within the vessel wall. In addition, a fluorodeoxyglucose-PET scan can detect increased metabolism of an inflamed vessel wall and provides a functional image of inflammation. Indeed, several case reports describe the potential of a fluorodeoxyglucose-PET scan to detect TA or GCA of large sized vessels.<sup>21-23</sup> This case illustrates that imaging techniques such as multislice CT scan, MR angiography, and fluorodeoxyglucose-PET scan have the potential to detect subclinical prestenotic large vessel vasculitis, as seen here in the aorta and carotid artery, beside its stenotic and occlusive form, as seen here in the pulmonary artery.

Laboratory parameters are of little help for the diagnosis of TA and GCA because specific laboratory tests are lacking. A raised erythrocyte sedimentation rate is pathognomonic for GCA and also found in most cases of TA. Mild to moderate anaemia is usually found in both types of vasculitis, white blood counts are normal. Given the absence of specific autoantibodies for the diagnosis of TA and GCA, these variables do not strikingly improve the diagnosis or classification of large vessel vasculitis. On the other hand, abnormalities of the cellular immune system and the cytokine milieu are poorly investigated. T cells are present in large quantities in the granulomatous lesions, and in our patient both CD4+ and CD8+ T cells were abundantly found in the periphery of granulomas. The role of these T cells may not be restricted to antigen recognition but may also lie in the production of proinflammatory cytokines. The production of TNF $\alpha$  was markedly increased in CD4+ and CD8+ T cells of the peripheral blood compared with healthy subjects, and most importantly, treatment normalised TNF $\alpha$  production by T cells. Other cytokines such as IL4, IL6, IL10, IL13, or interferon  $\gamma$  did not show this dramatic change. Apart from TNF $\alpha$ , only IL2 was raised in peripheral T cells, probably indicating an increase of T cell clones in TA. This increased IL2 production normalised after the start of treatment. We do not know if these restricted changes of the cytokine pattern of T cells are also found in classical cases of TA or GCA, but they might give not only an interesting insight into the disease pathogenesis but may also help to classify atypical cases of large vessel vasculitis.

This issue may be also true for the unusual observation of an up to 10-fold increase of peripheral CD4/CD8 double positive T cells, which are considered as immature T cells and are normally found only in small quantities in the peripheral blood. Assessment of T cell surface markers seems a useful tool to discriminate between this case and sarcoidosis, because sarcoidosis shows an enlarged CD4+ T cell subset, increasing the CD4/CD8 T cell ratio from 4:1 up to 10:1. In contrast, the CD4+ T cells subset was not enlarged in this patient; there was even a slight shift in favour of CD8+ T cells (CD4/CD8 ratio 1.5:1), making the diagnosis of sarcoidosis unlikely. This seems important because the histological features of sarcoidosis are similar to the one found in TA or GCA and a concurrence of sarcoidosis and TA-like aortitis has been reported.<sup>24, 25</sup>

In conclusion, we have presented a case of granulomatous large vessel vasculitis which leads to serious classification problems. Although this case fulfils the ACR criteria for GCA, it is in many senses atypical of GCA and shares common fea-

tures with TA. TA has been described as the great imitator, because of its protean clinical manifestations.<sup>26</sup> This case mirrors these findings very nicely, because it appears to combine an advanced stenotic stage of TA in the pulmonary circulation with a prestenotic stage in the systemic circulation. New imaging techniques and the systematic assessment of changes of the cellular immune system, such as T cell cytokine production, may help to classify other complicated cases of large vessel vasculitis and thus may contribute to an earlier diagnosis and effective treatment.



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