CASE REPORT

Takayasu's arteritis occurring under TNF- α blockers: a new paradoxical effect?

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SUMMARY

Takayasu's arteritis (TA) is a rare granulomatous vasculitic disease. Recently, experimental studies and several case reports have supported the use of anti-tumour necrosis factor (TNF) therapy for severe forms of TA. We report a case of a 58-year-old woman who was followed for spondyloarthritis. Her disease was resistant to non-steroidal anti-inflammatory drugs, and TNF- α blockers were initiated. The patient developed asthenia and severe back pain. The erythrocyte sedimentation rate was 82 mm and C reactive protein was 192 mg/L. Based on thickened walls of large vessel on MRI, a diagnosis of TA was established. Under corticosteroids and after discontinuation of TNF- α blockers, the patient remained free of symptoms at 8-month follow-up.

BACKGROUND

Takayasu's arteritis (TA) is a granulomatous inflammatory vasculitis of unknown aetiology that produces arterial stenosis and aneurysms; it primarily involves the thoracoabdominal aorta and its branches and the pulmonary arteries. Its association with spondyloarthritis is well documented. Conventional treatment consists of glucocorticoids. However, in the past few years, experimental studies and several case reports have supported the use of anti-tumour necrosis factor (TNF) therapy for resistant forms since TNF- α plays a key role in the formation of granuloma.^{1 2}

In the present report, we describe a case of TA induced by TNF blockers in a patient with spondyloarthritis.

CASE PRESENTATION

A 58-year-old Tunisian woman was suffering from inflammatory back pain and anterior chest wall for 2 years. The sternoclavicular joints were painful and swollen on examination. The erythrocyte sedimentation rate (ESR) was 35 mm and C reactive protein (CRP) was 12 mg/L. Spine and pelvic MRI showed bilateral inflammatory sacroiliitis and arthritis of the sternoclavicular joints. The diagnosis of spondyloarthritis was established according to Assessment of SpondyloArthritis international Society (ASAS) criteria.³ Despite testing four classes of non-steroidal anti-inflammatory drugs (NSAIDs), the patient remained extremely disabled with active disease as attested by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which was at seven. A cervicothoracoabdominal pelvic CT was performed and was normal. The ESR was 30 mm and the CRP was 6 mg/L. Etanercept therapy was then initiated. This treatment was

interrupted after the 10th injection for inefficiency. Indeed, the patient was still suffering from the inflammatory back pain, her BASDAI was at 6, the ESR was 39 mm and the CRP was 14.8 mg/L. A switch to adalimumab was made. A few days after the third injection, the patient presented asthenia, anorexia and widespread inflammatory pain in her buttock, shoulders and anterior chest wall. She had neither fever nor lymphadenopathies.

INVESTIGATIONS

The ESR was 82 mm and the CRP 192 mg/L. Tuberculin skin and QuantiFERON tests were negative. Neoplasia markers were within the normal range (ACE, CA 19-9). The mammography did not show any abnormality. Bone scintigraphy showed hyperfixation at the spine and sternoclavicular joints, consistent with a diagnosis of spondyloarthritis. A cervicothoracoabdominal pelvic CT was performed a year after the first one. It was normal apart from the thoracic level, which showed aortic and supra-aortic trunk parietal thickening that did not previously exist (figure 1). An angio-MRI confirmed the thickening of the thoracic aorta, which was extended to the infrarenal aorta, the common carotid arteries, the subclavian and humeral arteries, and the common femoral arteries with a 4 cm dilation of the ascending aorta (figure 2). Renal and pulmonary arteries were normal. Resuming the clinical examination, the right radial and humeral pulse was not found and a difference of 15 mm Hg in systolic blood pressure between the two arms was noted. An ophthalmological examination did not find retinal vasculitis. EEG and echocardiography were normal. A diagnosis of TA was established according to American College of Rheumatology (ACR 1990) criteria (3 criteria).⁴

DIFFERENTIAL DIAGNOSIS

Owing to the age of our patient, diagnosis of giant cell arteritis (GCA) was suspected. However, given the absence of headache, typical rheumatic joint pain, the presence of temporal pulse, the normality of the temporal artery Doppler and the possibility of occurrence of late TA, late onset TA was the most likely diagnosis.

TREATMENT

Adalimumab was stopped and the patient received corticosteroids (1 mg/kg/day) with a good response.

OUTCOME AND FOLLOW-UP

The patient is free of symptoms at 8-month follow-up.

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Comparison between the old and the latest CT scan.
Aortic (↔) and supra-aortic trunks parietal thickening (↔)

Figure 1 Comparison of the older and the latest CT scan: aortic and supra-aortic trunk parietal thickening.

DISCUSSION

Plasma levels of TNF- α are high in TA as well as GCA. In our patient the diagnosis of GCA was first suspected, especially as a new onset of GCA occurring under TNF blockers had been already reported.⁵ However, our patient met the diagnostic criteria for TA in addition to the absence of decisive arguments in favour of GCA, including the normality of the temporal arteries Doppler. Since plasma levels of TNF- α are high in TA, there are a large number of case series and observational studies supporting the premise that TNF inhibitors are highly effective and safe in patients with severe and refractory TA, with prolonged sustained response.¹⁻⁶ However, anti-TNF are currently recommended for the treatment of TA in cases of cortico-dependent or cortico-resistance despite treatment with a non-biological immunosuppressive medication.⁷ On the other hand, coexistence of rheumatic diseases and TA is rare but well described. To the best of our knowledge, overall, 16 cases of association of TA and spondyloarthritis have been reported in the literature.⁸ The concurrence of these two diseases existed without any immune modulating therapy. However, in the case we describe here, TA occurred shortly after the initiation of the TNF- α inhibitors

prescribed for treating active and resistant spondyloarthritis. This raises the problem of the relationship between TA and anti-TNF- α therapy. It was presumed in our case that this treatment was the most likely cause of TA since the first CT scan, which was performed before instauration of TNF- α blockers, did not show any sign of vasculitis. Similar cases of TA induced by TNF blockers have been reported in the literature.⁹⁻¹⁰ To the best of our knowledge, only two cases of TA induced by TNF- α inhibitors in patients with rheumatic disease have been described: one of seropositive rheumatoid arthritis (RA) and the other of spondyloarthritis.¹¹ The TA appeared under adalimumab in the case of RA and under golimumab in the case of spondyloarthritis.¹¹ As there is compelling evidence that TNF inhibitors are highly effective in refractory and relapsing TA,^{6,7} the occurrence of TA can be considered as a paradoxical side effect of anti-TNF agents. It must be remembered that the paradoxical effect is defined by the development of immune-mediated inflammatory disorder after the initiation of TNF inhibitors normally used to treat such disorders.¹² It is worth mentioning that paradoxical vasculitis is mainly limited to the skin, but in some cases,

Figure 2 Parietal wall thickening attaining aorta, proximal common carotid and subclavian arteries.

patients may experience the onset of an authentic systemic disease with renal, pulmonary and peripheral neuropathy, and central nervous system involvement.¹³ The mechanism of this paradoxical side effect remains unclear and the contribution of TNF- α inhibitors to the development of vasculitis cannot be determined but might be related to an imbalance of cytokines induced by the inhibition of TNF activity in predisposed individuals.¹⁴ Features suggesting a causal link between anti-TNF and

the onset of vasculitis include the short time from biological initiation to vasculitis onset, as in our case, and the favourable outcome after discontinuation of the TNF antagonist.¹⁵ Indeed, in all cases reported in the literature, as in our case, a positive response was observed after beginning corticosteroids and stopping anti-TNF.^{9–11}

Competing interests None.

Patient consent Obtained.

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Learning points

- Consider Takayasu's arteritis as a possible paradoxical effect of tumour necrosis factor (TNF)- α inhibitors.
- Corticosteroids combined with discontinuation of the anti-TNF- α leads to good results.
- Further randomised controlled clinical trials are necessary to investigate possible immune reactions associated with TNF- α blockers.

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