Reumatismo, 2024; 76 (4): 298-302

Cervical myelopathy as an atypical presentation of antineutrophil cytoplasmic antibody-associated vasculitis in a patient affected by silicosis: a case report and literature overview

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SUMMARY

We describe the case of a 76-year-old man affected by pneumoconiosis, secondary to silica dust exposure, who was diagnosed with antineutrophil cytoplasmic antibody (ANCA)-positive microscopic polyangiitis (MPA)-related cervical myelitis. Pneumoconiosis is reported to trigger autoantibody production and the onset of different autoimmune diseases, including ANCA-associated vasculitis (AAV). MPA is an AAV of the small vessels that can often affect the nervous system, although involvement of the spinal cord in the form of myelitis is described as an anecdotal occurrence. Our experience suggests that an autoimmunity workup should be considered for patients with pneumoconiosis who present with neurological symptoms consistent with AAV.

Key words: *ANCA vasculitis, pneumoconiosis, myelitis.*

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INTRODUCTION

Patients with pneumoconiosis show a high prevalence of systemic autoimmune rheumatic diseases (SARDs) and autoantibodies positivity, including antineutrophilic cytoplasmic antibodies (ANCA); in particular, the association between SARDs and occupational exposure to silica dust is well known (1). Indeed, through a dose-related effect, silica triggers autoantibody production and induces an imbalance between responders and regulatory T cells, leading to a dysregulation of the autoimmunity system. On the other hand, microscopic polyangiitis (MPA) is an ANCA-associated vasculitis (AAV) of the small vessels mostly involving lungs, kidneys, and skin; neurological involvement is reported in 55-79% of cases in the form of peripheral neuropathy (2), while the central nervous system (CNS) is rarely affected, and a clinical presentation as myelitis has been described in only three cases so far. Our case report sheds light on two uncommon and scarcely known occurrences in rheumatological practice: the onset of an AAV as a cervical inflammatory myelitis without meningeal involvement, and the association between AAVs and silicosis.

CASE REPORT

Herein we describe the case of a male patient presenting with cervical myelopathy and asymptomatic polyneuropathy as the onset manifestation of AAV.

A 76-year-old male patient was transferred to the Emergency Department of our University Hospital due to the acute onset of severe neck pain radiating to the upper and lower limbs, accompanied by acute urinary retention. Past pathological anamnesis was negative for noteworthy diseases, but the patient reported having worked as a quarryman for about 40 years. The neurological examination revealed mild muscle weakness on the right side (as evidenced by Min-

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gazzini's maneuvers), weak osteotendinous reflexes of the left leg, and normal cerebellar tests but multidirectional fluctuations at the Romberg test. He did not complain about sensitivity loss but referred mild paresthesia in both arms. Routine blood tests, as well as inflammatory markers (C-reactive protein), were normal. Magnetic resonance imaging (MRI) of the cervical spine (Figure 1a) demonstrated focal signal alterations in the spinal cord spanning from C2 to C4, with associated gray matter involvement. Additionally, there appeared to be partial contrast enhancement at C3 level, while the integrity of the meninges was preserved. The patient was therefore transferred to the Neurology Unit and promptly received intravenous steroid treatment (dexamethasone 8 mg daily), leading to a rapid improvement of symptoms.

During hospitalization, further examinations were performed. Neoplastic and common infective markers were negative, as well as cerebrospinal fluid analysis, which showed only a slight increase in glucose. In the urine analysis, no abnormalities were detected. Furthermore, there were no discernible signs or symptoms suggestive of involvement of the ear, nose, and throat (ENT) regions. Renal function was preserved, and circulating precipitins were absent. An autoimmunity workup highlighted the positivity of antinuclear antibodies 1:320 and ANCA, in particular anti-myeloperoxidase (MPO).

An electromyography (EMG) showed findings compatible with a severe demyelinating sensorimotor polyneuropathy, while a chest high-resolution computed tomography (Figure 1b), requested in light of the patient's employment history, showed multiple subpleural and centrilobular micronodules, partially confluent and principally located in both apices, fibrotic septal thickening, and bronchiectasis, consistent with silicosis. Bronchoalveolar lavage did not detect any pathological findings, while lung function tests highlighted a mild obstructive deficit and a decrease in carbon monoxide diffusing capacity.

After a collegial discussion between rheumatologists, radiologists, and pneumologists, a diagnosis of MPA anti-MPO+ associated with silicosis was made, while pulmonary vasculitis involvement was ruled out.

The patient was discharged with oral glucocorticoid therapy (50 mg/day prednisone (PDN) to be tapered) and subcutaneous methotrexate 15 mg/week together with prophylactic antiresorptive therapy. Considering the high infectious risk associated with silicosis and the absence of life-threatening complications, stronger immunosuppressive treatments were considered unnecessary.

At the 6-month follow-up, glucocorticoid therapy was tapered to 5 mg per day. The patient reported improvement in neurological symptoms with only residual persistent acral dysesthesia in the left hand and foot, while the neurological examination had returned to normal. EMG indicated remaining, though notably reduced, signs of sensorimotor polyneuropathy with demyelina-

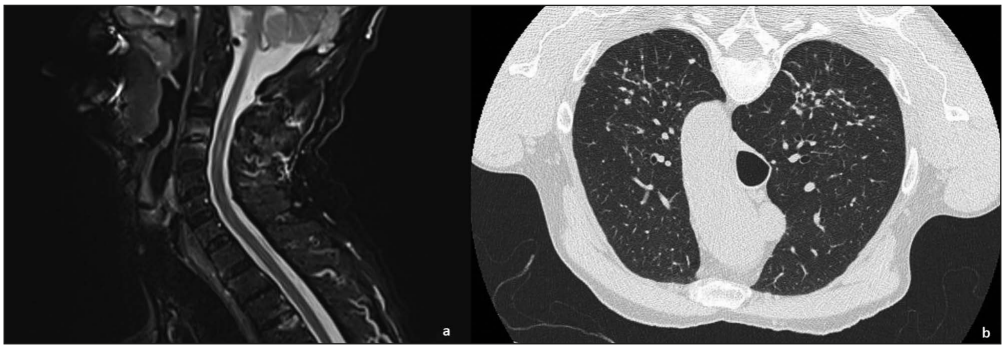

Figure 1 - A) Magnetic resonance imaging of the cervical spine (STIR sequence); B) pulmonary high-resolution computed tomography.

tion. MRI scans confirmed a decrease in the extent of the lesion at C2-C3 level and a complete resolution of myelitic involvement at C3-C4 level.

DISCUSSION AND CONCLUSIONS

This case report highlights two uncommon occurrences in rheumatology: the onset of an AAV as cervical inflammatory myelitis without meningeal involvement, and the association between AAVs and silicosis.

MPA is an AAV causing necrotizing inflammation of small blood vessels, with predominant manifestations affecting lungs, kidneys, and skin, even though neurologic involvement may occur. In AAV, nervous system involvement is reported in up to 55-79% of cases and mostly occurs in the form of peripheral neuropathy, with a higher incidence of mononeuritis multiplex in MPA and eosinophilic granulomatosis with polyangiitis (GPA) (3), while cranial neuropathy and CNS involvement are rare features, generally restricted to GPA patients with long-lasting disease (4). The spinal cord can be affected too, in the form of hypertrophic pachymeningitis (HP) (5), but very few patients experience HP as the first and only manifestation of the disease. Moreover, even though HP seems to be a peculiar feature of GPA, in an outdated case series (6) up to 43% of the patients displayed perinuclear ANCA positivity and a limited form of the disease, without extra-neurological involvement. However, it is worth noting that the real prevalence of ANCA-related HP might be underestimated due to the impossibility of applying classification criteria in such rare and complicated conditions, which are often classified as idiopathic HP (5). On the other hand, involvement of the spinal cord caused by dural or meningeal masses (necrotizing granulomas) as well as by subarachnoid hemorrhage is extremely rare (7, 8). Lastly, it appears that HP involvement is more common in the late stage of AAV and that CNS manifestations in general might prevail in the later stages of the disease (4).

The 2016 literature review by Decker *et al.* that collected reports of 20 patients with spinal cord involvement in MPA showed that most patients received at first either intravenous methylprednisolone or oral PDN. Of them, 13 patients also received cyclophosphamide as induction therapy, while maintenance consisted of either mycophenolate mofetil or azathioprine. 14/18 patients with available outcome data exhibited remission or disease improvement during follow-up (9). Ten patients underwent surgical intervention, which represents a crucial therapeutic strategy, especially when spinal cord compression is determined by spinal mass lesions, as further demonstrated by a recent case report by Yang *et al.* (10).

Specifically focusing on inflammatory myelitis, only three other cases (11-13) have been reported as a manifestation of an AAV: demographic and clinical data are reported in Table I.

Inflammatory myelitis seems to be associated with male gender and anti-MPO autoantibodies. A possible explanation of the low incidence of isolated inflammatory myelitis may be that spinal cord vascular supply is provided by medium-sized vessels (anterior spinal artery, posterior spinal arteries, and segmental medullary arteries) and that MPA usually affects capillaries. On the other hand, in GPA, spinal cord involvement is more commonly secondary to granulomatous inflammation of meninges or caused by spreading granulomatous tissue from contiguous ENT district.

We presented the clinical case of a patient affected by an extremely rare neurological manifestation of AAV and an even more unique combination with silicosis. We believe these data could expand the actual limited knowledge on such uncommon but clinically relevant matters. A history of silica exposure is a well-documented potential trigger for the development of autoantibodies such as ANCA and it has been reported to be associated with the onset of different autoimmune diseases, among which vasculitis. In addition, out of the only four known cases of AAV presenting with myelitis, two (50%) were affected by pneumoconiosis. We could speculate that the formation of ANCA in the blood enhanced by inhalation of certain kinds of dust and/or fibers might

Table I - Demographic and clinical data of patients.

Age (years), sex, author, year	Manifestations	Other	Antibodies	Diagnosis	Previous treatment	Treatment	Outcome
55, male, Martens (11), 1982	Cauda equina, peripheral neuropathy	–	ANCA nr	Disseminated GPA*	nr	PDN, CPA	Death
22, male, Reinhold-Keller *et al.* (12), 2001	ENT involvement, vision loss	–	ANCA -	GPA	–	PDN, CPA	Death
65, male, Hamilton *et al.* (13), 2011	Pulmonary and renal involvement	COPD, duodenitis pericarditis, asbestosis	pANCA, anti-MPO+	AAV*	PDN, CYC, MMF, AZA, RTX	PDN, RTX (failure), MMF (failure) PE	Remission after 3 relapses
76, male, our patient	Asymptomatic peripheral neuropathy	Silicosis	pANCA, anti-MPO+	MPA	–	PDN, MTX	Remission

ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; AZA, azathioprine; CPA, cyclosporine; COPD, chronic obstructive pulmonary disease; CYC, cyclophosphamide; ENT, ear, nose and throat; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; MPO, myeloperoxidase; MPA, microscopic polyangiitis; MTX, mehotrexate; nr, not reported; pANCA, perinuclear ANCA; PDN, prednisone; PE, plasma exchange; RTX, rituximab; *diagnosis made before nervous system symptoms onset.

represent a crucial pathogenetic moment in the development of myelitis probably through the secretion of proinflammatory cytokines, such as tumor necrosis factor and interleukin-1, leading to endothelial injury and dysfunction, procoagulant and proadhesive conditions for platelets and, ultimately, vasculitis of the spinal cord vessels (14). As previously stated, this could explain the rarity of its involvement in AAV and, more specifically, MPA, since these vasculitides primarily affect small-sized vessels and only occasionally medium-sized vessels. Regarding our case, compression of the spinal cord due to undergoing inflammation rather than an ischemic involvement could more likely explain the patient's clinical presentation. In fact, although MRI scans did not provide specific findings and a magnetic resonance angiography was not performed, the prompt and almost complete resolution of neurologic symptoms after the administration of glucocorticoid and immunosuppressive treatment reasonably rules out the presence of prominent ischemic damage. In conclusion, there might be a rationale for the search of ANCA-positivity in patients with previous exposure to silica who exhibit neurological symptoms and, secondly, that AAV represents a crucial differential diagnosis in patients presenting with HP and, despite less typical, isolated myelopathy. Indeed, early recognition of an underlying vasculitis could allow timely and proper clinical management through steroid treatment, increasing the chances of almost complete neurological recovery (12).

Contributions

SG, developed the initial concept of the study, collected relevant data, and reviewed the available literature; SG, RT, equally contributed to designing and drafting the article; EC, SB, revised the manuscript critically for important intellectual content; LC, BF, approved the final version of the article to be submitted. All authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Conflict of interest

The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate

Not applicable.

Informed consent

Patient's informed consent to use personal data was obtained.

Funding
None.

Availability of data and materials
Data are available from the corresponding author upon request.

Acknowledgments
The authors thank the patient for his willingness to cooperate.

REFERENCES

1. Gómez-Puerta JA, Gedmintas L, Costenbader KH. The association between silica exposure and development of ANCA-associated vasculitis: systematic review and meta-analysis. Autoimmun Rev 2013; 12: 1129-35.
2. Sassi SB, Ghorbel IB, Mizouni H, Houman MH, Hentati F. Microscopic polyangiitis presenting with peripheral and central neurological manifestations. Neurol Sci 2011; 32: 727-9.
3. Koike H, Nishi R, Ohyama K, Morozumi S, Kawagashira Y, Furukawa S, et al. ANCA-associated vasculitic neuropathies: a review. Neurol Ther 2022; 11: 21-38.
4. Shimojima Y, Kishida D, Ichikawa T, Kida T, Yajima N, Omura S, et al. Hypertrophic pachymeningitis in ANCA-associated vasculitis: a cross-sectional and multi-institutional study in Japan (J-CANVAS). Arthritis Res Ther 2022; 24: 204.
5. Shimojima Y, Sekijima Y. Hypertrophic pachymeningitis in ANCA-associated vasculitis: clinical and immunopathological features and insights. Autoimmun Rev 2023; 22: 103338.
6. Saeki T, Fujita N, Kourakata H, Yamazaki H, Miyamura S. Two cases of hypertrophic pachymeningitis associated with myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA)-positive pulmonary silicosis in tunnel workers. Clin Rheumatol 2004; 23: 76-80.
7. Wang DC, Wei JW, Liu JH, Hu YG. The upper thoracic spinal cord compression as the initial manifestation of Wegener's granulomatosis: a case report. Eur Spine J 2007; 16: 296-300.
8. Xie J, Jia E, Wang S, Yu Y, Li Z, Zhang J, et al. Relapsing subarachnoid hemorrhage as a clinical manifestation in microscopic polyangiitis: a case report and literature review. Clin Rheumatol 2022; 41: 3227-35.
9. Decker ML, Emery DJ, Smyth PS, Lu JQ, Lacson A, Yacyshyn E. Microscopic polyangiitis with spinal cord involvement: a case report and review of the literature. J Stroke Cerebrovasc Dis 2016; 25: 1696-704.
10. Long Y, Zheng Y, Chen M, Zhang B, Gao C, Gao Q, et al. Antineutrophil cytoplasmic antibodies in patients with idiopathic inflammatory-demyelinating diseases. Neuroimmunomodulation 2014; 21: 297-303.
11. Martens J. Spinal cord involvement in Wegener's granulomatosis. Clin Rheumatol 1982; 1: 221.
12. Reinhold-Keller E, de Groot K, Holl-Ulrich K, Arlt AC, Heller M, Feller AC, et al. Severe CNS manifestations as the clinical hallmark in generalized Wegener's granulomatosis consistently negative for antineutrophil cytoplasmic antibodies (ANCA). A report of 3 cases and a review of the literature. Clin Exp Rheumatol 2001; 19: 541-9
13. Hamilton AJ, Whitehead DJ, Bull MD, D'Souza RJ. Systemic panca-associated vasculitis with central nervous involvement causing recurrent myelitis: case report. BMC Neurol 2010; 10: 118.
14. Weidner S, Hafezi-Rachti S, Rupprecht HD. Thromboembolic events as a complication of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Care Res 2006; 55: 146-9.