A Neurological Complication in Rheumatoid Arthritis – A Scenario of Catastrophic Proportions

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Abstract

Background: Rheumatoid Arthritis (RA) is a common systemic inflammatory disease that can present with a plethora of extraarticular manifestations. Many patients with RA from low- and middle-income countries do not get timely and adequate treatment with disease-modifying therapies. This results in the perpetuation of a chronic inflammatory state. **Focus:** Rheumatoid vasculitis (RV) is one of the most aggressive complications of RA resulting from a prolonged proinflammatory milieu. Usually, it has the involvement of multiple organ systems, with cutaneous manifestations being the most common. Neurological presentation is uncommon but severe when present. **Highlight:** We present a case of severe RV presenting with an unexpected neurological complication consisting of cranial and peripheral neuropathy with small vessel disease and intracerebral haemorrhage. We intend to highlight the morbidity and long-term consequences of inadequately treated RA, the most common inflammatory disease of the connective system especially in light of the neurological presentation.

Keywords: Axonopathy, motor neuron, motor neuropathy, neuronopathy, rheumatoid arthritis, rheumatoid vasculitis, vasculitis

Clinical History and Findings

A 52-year-old lady with a 20-year history of untreated Rheumatoid Arthritis (RA) presented to us with weight loss of over 35 kilos over the preceding 2 years and asymmetric onset weakness of extremities involving all four limbs over 1 year. At the same time, she also had difficulty in swallowing and speaking along with behavioural changes consisting of apathy, withdrawn behaviour and sadness of mood with crying spells. This had progressed to such an extent that she remained confined to bed, requiring help for performing all activities of daily living. At the time of the presentation, she didn't have any pre-existing comorbidities (Diabetes mellitus, Dyslipidemia or hypertension).

On evaluation, she was found to be of low nutritional status with a weight of 45 kilos and loss of buccal pad of fat. The total number of swollen joints was 17, with wrist and finger deformities characteristic of RA as depicted in Figure 1a. Her CDAI, DAS 28 and SDAI scores for RA were 18.5, 4.9 and 21 points, respectively, suggestive of moderate disease activity.

The neurological evaluation showed a Mini-Mental State Examination score of 16/30. Detailed lobar assessment showed frontal subcortical and temporal lobe dysfunction. She had lower motor neuron weakness of bilateral facial and bulbar muscles [Figure 1b]. There was generalized wasting predominantly distal with bilateral wrist and foot drop and partial clawing of digits. Weakness of the proximal group of muscle, trunk and neck extensors was also present to a lesser extent. All reflexes were preserved with flexor plantar. She localized pain with a preserved joint position in larger joints. The rest of the systemic examination was within normal limits.

Laboratory Findings

Her ESR and CRP were both elevated (86 mm in the first hour and 10.2 IU, respectively) and the quantitative values of Rheumatoid factor (RF) and Anti-CCP levels were 1270 IU/ml and 98 units, respectively. Anti-nuclear antibodies were positive with a 2+ strength and nuclear fine-speckled pattern (Supplement 1, Table1). The remaining laboratory parameters were normal. A nerve conduction study showed reduced CMAP amplitude in the bilateral median, ulnar, tibial, and peroneal nerves with normal SNAP amplitude in all tested nerves [Supplement 1, Table 2] X-ray of bilateral hands and feet showed bony deformities with diffuse osteopenia and articular erosion typical of RA as depicted in Figures 1c and 1d. A nerve-muscle biopsy (from the superficial peroneal nerve and peroneus longus muscle) showed evidence of dense perivascular inflammation in the epineurium with prominent transmural inflammation involving larger arteriole with focal neovascularization, perineurium was unremarkable. Endoneurium showed moderate to marked multifocal loss of myelinated

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nerve fibres suggestive of vasculitic neuropathy with muscle showing preserved fascicular architecture and polygonal myofibres with mild variation in fibre size with peripherally placed nuclei, there were no features of active myopathy [Figure 1e and f]. Owing to her cognitive deficits, MRI of the brain was done that showed small vessel disease in bilateral periventricular areas with Fazekas grading 3 [Figures 2a and b]. CT angiography of cerebral blood vessels as depicted in Figure 2c was normal.

Treatment and Follow-Up

As per the history, clinical examination, and laboratory findings, the possibility of Systemic Rheumatoid Vasculitis (RV) was considered in our patient. The brunt of the disease was on the neuraxis apart from the musculoskeletal manifestations.

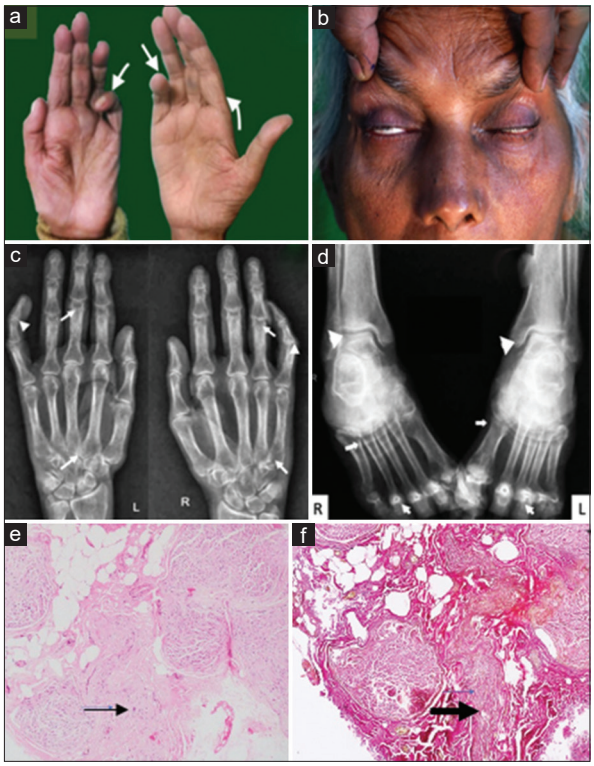

Figure 1: (a). Depicts RA-associated hand deformities, right hand shows boutonniere deformity (white arrow) and the left hand had a Mallet finger (white arrow) along with ulnar deviation of the hand (curved arrow), associated wasting of small muscles of the hands seen. (b). Shows bifacial LMN type of weakness. (c). X-ray of bilateral hands showed erosions and subchondral sclerosis (arrows) with loss of joint cavity along bilateral proximal interphalangeal joints and carpometacarpal joints. There are subluxations (arrowheads) present along bilateral proximal interphalangeal joints of the fifth digit of both hands. (d). X-ray of bilateral feet AP view shows diffuse osteopenia of metatarsal and phalangeal bones with articular erosions (white arrows) at metatarsophalangeal joints and reduced intertarsal joint space (arrowhead) with bilateral hallux valgus. (e). HPE transverse section of the nerve biopsy shows an obliterated vein in the epineurium with marked hyalinization of the wall (black arrow, Haematoxylin and Eosin, X100). (f). HPE transverse section of nerve biopsy Elastic Van Gieson stain highlights the obliterated vein (X100, black arrow). LMN: Lower motor neuron, HPE: Histopathological examination

Other differentials were ruled out by the detailed tests [Supplement 1, Table 1].

She received parenteral followed by oral steroids and monthly injectable cyclophosphamide to induce remission. There was mild improvement in her wrist drop and significant improvement in pain and swelling in the joints. Clinical improvement correlated with a decrease in the values of inflammatory markers [Supplement 1, Table 1] Low-dose aspirin and Donepezil were added for the cerebral small vessel disease along with antidepressants, and there was an improvement in her cognition and mood. Three months after her last cycle of cyclophosphamide she developed sudden onset of right hemiparesis that was evaluated to reveal a left putaminal bleed [Figure 2d] ICH score was zero. Aspirin was discontinued and blood pressures were monitored, and she was started on an angiotensin receptor blocker. She was discharged with advice for continuing physiotherapy and medications and continues to remain in follow-up without any further events.

Discussion

Our patient had a long history of untreated RA with evidence of cranial neuropathy, peripheral neuropathy and cognitive decline complicated by intracerebral haemorrhage. She had high titres of RF, with histopathology showing extensive vasculitis in the nerve biopsy. There is a high burden of diagnosed and undiagnosed RA in countries like India, which also has one of the highest rates of Disease Adjusted Life Years (DALY) in the world.[1] A disease of sufficiently long duration can cause severe disease of the joints as was seen in our patient. However, the tendency to consider longstanding RA as a burnt-out disease is not only misleading but also detrimental. A study showing

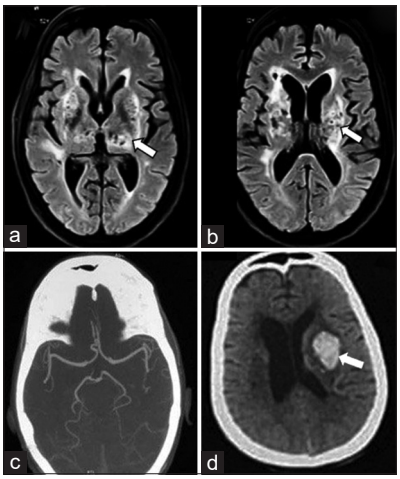

Figure 2: (a) & (b). Depicts chronic small vessel disease changes in axial T2Flair MRI sequence as multiple confluent hyperintensities in bilateral periventricular deep white matter area of the frontotemporal lobe, thalami and basal ganglia regions (black arrow) along with the presence of Virchow-Robbin spaces. (c). CT angiography axial cut of cerebral vessels was normal. (d). NCCT Head axial cut shows left Putaminal haemorrhage (white arrow). MRI: Magnetic Resonance Imaging, FLAIR: Fluid Attenuated Inversion Recovery, NCCT: Non-Contrast Computed Tomogram

serial measurements of erythrocyte sedimentation rates (ESR) to monitor disease activity in RA showed a nonlinear reduction in values in the initial phases followed by a relative plateau and a subsequent rise over time. This study proved that disease activity was programmed early in the course of the disease and that there is no real 'burnt-out phase' of the condition as is widely believed.[2] Chronic complications like RV can arise out of long periods of untreated disease as happened with our patient.[3]

It is also essential to review the implications of RV due to the high burden of untreated disease in many countries.[4,5] Whereas overall extraarticular manifestations have been reported in up to 40.6% of patients of RA[6] with peripheral nerve involvement reports varying from 17%[7] to 33%,[8] RV is said to complicate only about 1% of patients with RA.[9] It affects small- and medium-sized vessels. Male gender, long-standing disease and smoking are some of the predictors for the development of RV, as also an association with HLA-DRB1*04 alleles. It is often accompanied by an increase in titres of acute phase reactants and RA factor.[10] Peripheral nerve involvement in RA usually occurs as mono neuritis multiplex, extensive mononeuritis, cutaneous neuropathy and polyneuropathy.[6,11] Pathology in RV is suspected to be ischemic occlusion of the vasa nervorum, whereas deposition of circulating immune complexes, cryoglobulinemia, and complement cascade activation is also thought to play a part. Inflammatory cell infiltrates are usually present but not essential for diagnosis.[12] Microaneurysms are usually not seen.[11] A study of 32 patients with RA and necrotizing vasculitis in nerve biopsy revealed epi and perineural vasculitis and axonal degeneration in up to 77% of the nerve fibres. The overall survival rate in these patients was 57% at 5 years.[13]

Many times, RV is said to occur in patients with a supposed 'burnt out' RA, but in these stages, it is associated with highly raised titres of RF and antibodies to the cyclic citrullinated peptide (anti-CCP) suggesting the disease to be immune complex mediated.[14] We would like to bring out the fact, in a long-standing disease course as in our case with clinical disease activity score in the moderate-severe range was thought to be burnt out and left untreated by the physician showed the presence of ongoing inflammation (raised titres of RF and anti-CCP Ab) and manifested as systemic and cerebral RV. Cutaneous disease is usually the most common manifestation of RV with ischemic ulcerations of the extremities, digital infarcts, etc.[11] Predominant neurological disease in RV without cutaneous manifestation is very rarely reported in the literature.

Vasculitis could be the only explanation for extensive leukoaraiosis in the brain. CT angiography of brain vessels was normal, but we could not proceed with a more sensitive test like digital subtraction angiography of cerebral vessels or brain biopsy due to lack of consent. It is important to note that a normal CT angiography of cerebral vessels cannot rule out vasculitis and diagnosis had to rely on histopathological changes. CNS involvement has been very rarely reported in patients with RV[15] and intracerebral haemorrhage has only been reported with the presence of hypertension.[16] The clinical presentation is varied in cerebral RV ranging from vascular headaches, seizures, cranial neuropathies or cerebrovascular events.[17] Marked inflammatory response in long-standing RA cases causing intimal damage and arteriosclerosis had been implicated as the possible mechanism for cerebrovascular events occurring in RA patients.[18] Literature is very scanty about the coexistent central and peripheral disease and our patient is possibly the first patient with such an extensive neurological presentation of RV sparing the more common cutaneous and other visceral manifestations of the disease.

Evidence of systemic vasculitis carries high morbidity, and B cell depleting therapy (Rituximab) or cyclophosphamide are the mainstays of management.[19] Currently, there is no consensus therapeutic regimen for managing cerebral RV. Aggressive treatment with steroids in combination with second immunomodulation (Cyclophosphamide, B cell depleting therapy or TNF-alpha inhibitors) should be considered. No randomized trials have been conducted to determine the choice of one immunomodulation over the other. In a study by Puéchal *et al*.,[20] management of systemic RV with Rituximab had shown complete remission in 75% of cases with a reduction in steroid dependence. Still, significant improvement is uncommon, and increased morbidity is seen in advanced cases. In our patient, we planned pulse intravenous cyclophosphamide based on her clinical presentation and histopathological findings.

Conclusion

It is crucial to rule out vasculitis in patients with longstanding RA presenting with new onset neurological deficits and raised titres of RA factor and anti-CCP. It is important to note that vasculitis can present anywhere in the neuraxis with cerebral small vessel disease, cranial, and peripheral neuropathy, and strokes as seen in our patient.

Key points

- Labelling longstanding RA as a 'burnt-out disease' is misleading as vasculitis is one of the most catastrophic presentations occurring in longstanding RA.
- The persistence of high titres of inflammatory markers (ESR and CRP) in longstanding RA should raise suspicion for RV in the presence of new-onset neurological deficits.
- RV necessitates aggressive therapy over the standard use of disease-modifying agents for RA.

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Conflicts of interest

There are no conflicts of interest.

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Supplement 1

Table 1: Diagnostic Workup

Laboratory investigation	Results	
	Work Up (Pre-Treatment)	Follow up (post treatment)
Hemoglobin (gm/dl)	11.7	
ESR	86mm 1st hr	40mm 1st hr
CRP	10.2	4.8
RA Factor	1270 IU/ml (0-15)	340IU/ml
Anti CCP level	98	
Anti Ro and Anti La	Negative (<0.03)	
UPEP/SPEP	Negative	
Amyloid fat pad biopsy	Negative	
Serum cryoglobulin level	Normal	
Autoimmune/Paraneoplastic panel	Negative	
ANA	positive, 2+, nuclear, fine speckled	
ANCA	less than 0.2 IU/ml	

CECT Chest – No evidence of interstitial lung disease

Table 2: Electrophysiological study of motor and sensory nerves

Nerve	Motor Distal latency (ms)	CMAP Amplitude (mV)	Conduction Velocity (motor) (m/s)	SNAP Amplitude (microvolt)	Conduction Velocity (sensory) (m/s)	Fwave (ms)
Rt Median	3.28	5.1	63	79.5	59	25.59
Left Median	2.66	6.9	56	102.7	64	26.0
Right ulnar	2.60	3.0	62	32.5	60	-
Left ulnar	2.40	1.2	50	59.5	52	-
Right tibial	3.85	2.4	39	-	-	45.8
Left tibial	3.54	2.1	44	-	-	48.9
Right peroneal	4.32	1.8	46	-	-	-
Left peroneal	4.79	2.6	47	-	-	-
Right sural	-	-	-	13.4	46	-
Left sural	-	-	-	16.9	62	-