Rhabdomyolysis in a Patient with Polyarteritis Nodosa

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Abstract:
Polyarteritis nodosa (PAN) is a medium vessel vasculitis affecting systemic organs. Muscle involvement of PAN usually lacks elevation of creatinine kinase (CK). We herein report a case of PAN with rhabdomyolysis. A 71-year-old man was hospitalized because of muscle weakness of the lower limbs that persisted for 1 month. On a physical examination, rapidly progressive lower proximal muscle weakness and bilateral drop foot were observed. His blood test showed an elevation in the C-reactive protein (19.5 mg/dL) and CK (13,435 IU/L) levels and negativity for anti-neutrophilic cytoplasmic antibody. Computed tomographic angiography showed stenosis of the left renal artery. Electromyogram indicated mono-neuritis multiplex pattern, and enhanced magnetic resonance imaging demonstrated discretely granular hyperintensities on T2 and slow tau inversion recovery in his femoral muscles. A femoral muscle-biopsy specimen showed fibrinoid necrosis of medium-sized vessels and disruption of the elastic lamina of the vessel wall in fascia. Furthermore, muscle necrosis was localized depending on the arterial distribution, suggesting ischemic changes in the muscles. Given these findings, he was diagnosed with PAN with rhabdomyolysis and treated with methyl-prednisolone pulse therapy followed by oral prednisolone at 50 mg/day. He was additionally treated with monthly intravenous cyclophosphamide at 500 mg. Sustained remission has been obtained for two months since the treatment. Although rhabdomyolysis rarely manifests with PAN, it should be included in a differential diagnosis of febrile patients presenting with acute myalgia and weakness with CK elevation.

Key words: polyarteritis nodosa, muscle involvement, rhabdomyolysis

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Introduction
Polyarteritis nodosa (PAN) is a medium-sized vessel vasculitis that usually affects systemic organs (1). A number of studies have shown that muscle involvement is relatively common in this entity (2, 3). Although the main clinical feature is severe myalgia, it presents without elevation of creatinine kinase (CK). It has been reported that intense fasciitis may be the cause of severe muscle pain induced by medium-sized vasculitis in muscles, suggesting that muscle destruction is rarely manifested. We herein report a rare case of PAN with rhabdomyolysis.

Case Report
A 71-year-old man was hospitalized because of a month-long history of muscle weakness in his lower limbs. He had no history of statin use prior to admission and had longstanding tobacco use. At admission, his body temperature was 36.3°C, blood pressure 187/105 mmHg, heart rate 64/minute, and respiration rate 20/min. On a physical examination, fine crackle was observed in the bilateral lower chest, and bilateral proximal muscle weakness in the lower extremities and bilateral foot drop were observed. The laboratory findings were as follow: white blood cell count of 15,600/μL, Hg 12.2 g/dL, Plt 375×10³/μL, PT-INR 1.26,
Figure 1. Findings of computed tomography imaging and colonoscopy. Computed tomography showed interstitial lung disease at the bottom (A) and left renal artery stenosis (B, C). Multiple ulcerations were found by colonoscopy (D).

APTT 37.5 s, D-dimer 1.3 μg/mL, AST 73 IU/L, ALT 41 IU/L, ALP 505 IU/L, γ-GTP 89 IU/L, LDH 320 IU/L, UN 4.0 mg/dL, Cr 0.91 mg/dL, Na 141 mEq/L, K 4.2 mEq/L, Cl 101 mEq/L, aldosterone 54 pg/mL (normal range: 3-12 ng/mL), C-reactive protein (CRP) 19.5 mg/dL, CK 13,435 IU/L, myoglobin 424 ng/mL (normal range: <60 ng/mL), and KL-6 184 U/mL. The urinalysis showed potential blood in urine (3+) and a urinary red blood cell (RBC) count of 30-49/HPF. Urinary myoglobin was increased (9,859 ng/mL). Anti-nuclear antibody, anti-Jo-1 antibody, and anti-neutrophilic cytoplasmic antibodies were all negative. Infectious diseases, including hepatitis B virus, were excluded. Muscle weakness in the lower extremities developed even while he was in hospital. He also had hypertension, and computed tomographic (CT) angiography showed interstitial lung disease and left renal artery stenosis (Fig. 1A-C). Multiple ulcerations were found by colonoscopy, and only non-specific inflammatory changes were detected in a biopsy specimen from the ulceration (Fig. 1D). The specimens of a muscle biopsy revealed fibrinoid necrosis of the medium-sized arteries and disruption of the elastic lamina of the vessel walls in the perimysium (Fig. 3B). Focal muscle necrosis without inflammatory cell infiltration was observed along the course of the medium-sized arteries, indicating ischemia (Fig. 3C).

He was diagnosed with PAN based on the following clinical features and pathological findings: hypertension, renal artery infarction, gastrointestinal bleeding due to multiple colon ulcerations, mononeuritis multiplex, myalgia, muscle weakness, and fibrinoid necrosis of medium-sized vessels with disruption of the elastic lamina (4). Furthermore, Antons et al. recently defined rhabdomyolysis as muscle symptoms with marked CK elevation (>10 times the upper limit of normal) (5), and the present case satisfied this criterion. These findings led to the diagnosis of PAN with rhabdomyolysis.

Acute renal injury was prevented by three days’ hydration therapy. Although hematuria and an increase in the serum creatinine and LDH were seen at hospitalization, they improved within 1 week as follows: hematuria (3+) → (-), serum creatinine 0.91→0.77 mg/dL, and LDH 494→392 U/L. Angiotensin receptor antagonist (ARB) and calcium channel blocker (CCB) were initiated against hypertension, resulting in a normalized blood pressure from 187/105 to 120/68 mmHg over 2-week observation. However, the serum renin
level increased from 9.0 to 27.4 ng/mL·h during hospitalization.

His clinical course after immunosuppressive treatment is shown in Fig. 4. The patient was treated with methylprednisolone pulse therapy followed by prednisolone at 45 mg/day. Since a poor prognosis was expected at the initial assessment (6), he was also treated with 500 mg of monthly intravenous cyclophosphamide therapy. The proximal muscle disturbance and levels of CRP and CK were rapidly improved, but the muscle weakness in the tibiales anterior remained. Fig. 5 shows the post-therapeutic change in organ manifestations. Although we observed improvement of the discretely granular hyperintensities on STIR images in the femoral muscle by MRI and the ulceration of colon, the stenosis of the left renal artery and interstitial lung disease were not changed. He showed sustained remission for two months after the initial induction therapy.
Figure 4. Clinical course after the treatment. The patient was treated with methylprednisolone pulse therapy followed by prednisolone at 45 mg/day. He was also treated with 500 mg of monthly intravenous cyclophosphamide therapy. The proximal muscle disturbance and levels of CRP and CK were rapidly improved, although the muscle weakness in the tibiales anterior muscle remained. He showed sustained remission for two months after the initial induction therapy. PSL: prednisolone, mPSL: methylprednisolone, IVCY: intravenous cyclophosphamide, MMT: Manual Muscle Testing, TA: tibial anterior muscle, CK: creatinine kinase, CRP: C-reactive protein

Figure 5. Findings of computed tomography imaging, colonoscopy, and magnetic resonance imaging of the lower limbs after treatment. Although interstitial lung disease (A) and the stenosis of the renal artery (B, C) were not changed after the treatment, the multiple ulcerations of colon were improved (D). The discretely granular hyperintensities on STIR in femoral muscle were also improved (E). STIR: slow tau inversion recovery
Table. Comparison between Past Literature and Our Case.

| Baseline characteristics | Our case | Ref No.10 | Ref No.11 | Ref No.12 Case 1 | Ref No.12 Case 2 | Ref No.13 | Ref No.14 | Ref No.15 | Ref No.16 | Ref No.17 |
|--------------------------|----------|-----------|-----------|------------------|------------------|-----------|-----------|-----------|-----------|-----------|
| Age                      | 70       | 40        | 32        | 23               | 25               | 44        | 47        | 57        | 54        | 38        |
| Gender                   | M        | M         | F         | F                | M                | F         | M         | F         | F         | F         |
| Myalgia                  | +        | +         | +         | +                | +                | +         | +         | +         | +         | +         |
| Fever                    | -        | -         | +         | -                | +                | -         | +         | -         | +         | +         |
| ESR (mm/h)               | 75       | 24        | 115       | 89               | 40               | 46        | 106       | 96        | 86        | 87        |
| CRP (mg/dL)              | 19.4     | NA        | NA        | NA               | NA               | 3.43      | 21.6      | 21.6      | 21.6      | 21.6      |
| WBC (μL)                 | 15,600   | 5,000     | 12,900    | 9,300            | 16,870           | NA        | 9,700     | 10,000    | 19,000    | 10,400    |
| CK (IU/L)                | 1,451    | Normal    | SI        | SI               | SI               | Normal    | Normal    | Normal    | Normal    | Normal    |
| Treatment regimen        | PSL 50 mg| BM        | SI        | PSL              | SI               | Normal    | Normal    | Normal    | Normal    | Normal    |
|                          | IVCY 1.5 mg| 60 mg | SI        | PSL              | SI               | Normal    | Normal    | Normal    | Normal    | Normal    |
| Time to remission (day)  | 7        | 7         | 1         | 5                | 5                | 7 months  | 1-2       | 5         | 1         | 1         |

NA: not available, SI: slightly increased, ESR: erythrocyte sedimentation rate, CK: creatinine kinase, WBC: white blood cells, PSL: prednisolone, IVCY: intravenous cyclophosphamide

Discussion

Earlier studies have suggested that directed muscle biopsies reveal vascular inflammation in 65% of patients with PAN, and blinded muscle biopsies revealed vasculitis in up to one-third (2). As Pagnoux et al. (3) recently described, while muscle involvement is clinically common and almost 60% of patients with PAN report myalgia at the diagnosis, the pathogenesis of myalgia has not been elucidated. Since necrotizing vasculitis is usually detected in the fascia and the normal architecture of muscle fibers is preserved, intense fasciitis may be the cause of severe muscle pain (7). Some studies have reported MRI findings in affected muscles in PAN patients, including high intensity on T2-weighted imaging (WI) and gadolinium enhancement on T1WI, which suggests edema (8, 9).

A literature review found six cases of PAN complicated by muscle involvement (Table) (7, 10-17). The age of the onset varied from 23 to 57 years old, and no gender differences were seen. Most cases had elevated ESR levels, but no association with a fever was seen. A lack of CK elevation with myalgia was observed in all cases. Prednisolone was initiated in all cases at varying doses, and a relatively rapid clinical response was obtained. Our case is unique in the elderly onset of the disease course and progression of rhabdomyolysis.

The histological findings in this case were consistent with medium-sized vasculitis in the perimysium. The widely extended distribution of muscle necrosis might suggest severe ischemia due to the severe involvement of a wider range of vasculitis in the medium-sized arteries. The severe muscle ischemia may have contributed to the CK elevation in this case.

Gallian et al. described hyperintense signals on T2WIs or STIR sequences in muscles of PAN patients without CK elevation, but the areas of involvement were relatively localized and mild compared to our case (8). Furthermore, Lega et al. recently reported that organ ischemic change due to systemic necrotizing vasculitis including PAN was associated with smoking or atherosclerosis (18). The disease onset of our case was older than in typical case (3), and long-standing tobacco use was documented in his history. In addition, multiple calcifications of arteries were found on CT angiography, indicating relatively severe atherosclerosis. Taken together, these findings suggest that the extent of the severe inflammation and atherosclerotic change of vessels in our patient may have led to rhabdomyolysis.

Both PAN and atherosclerosis contributed to the pathogenesis of this case. Although a therapeutic response was clearly seen in the ulceration of the colon and rhabdomyolysis, the stenosis of the left renal artery was unchanged. We therefore speculated that the contribution of atherosclerosis might be more dominant in the stenosis of the left renal artery than in the ulceration of the colon and rhabdomyolysis.

In summary, we encountered a PAN patient with rhabdomyolysis. The extent of vasculitis, the severity of the inflammation, and atherosclerotic change may have induced the unusual ischemic characteristics noted here.

The authors state that they have no Conflict of Interest (COI).

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