Polymyositis with elevated serum IgG4 levels and abundant IgG4⁺ plasma cell infiltration
A case report and literature review

Ryusuke Anan, MD, Mitsuhiro Akiyama, MD, PhD, Yuko Kaneko, MD, PhD, Jun Kikuchi, MD, PhD, Kazuho Suzuki, MD, Shiro Matsubara, MD, Tsutomu Takeuchi, MD, PhD

Abstract
Introduction: Polymyositis (PM) is a type of autoimmune, inflammatory myopathy. IgG4-related disease (IgG4-RD) is a recently recognized disease entity characterized by elevated serum IgG4 levels and IgG4⁺ plasma-cell infiltration of various organs. However, several reports have described cases of other diseases that present with those features, suggesting the importance of careful differential diagnosis. Herein, we report the first case of PM with elevated serum IgG4 levels and IgG4⁺ plasma cells in the muscles, mimicking IgG4-RD.

A 73-year-old woman visited our hospital because of proximal muscle weakness of both thighs. Her blood test showed high levels of serum creatinine kinase, aldolase, and IgG4. Magnetic resonance imaging of the thighs showed muscle edema. Needle electromyography showed findings typical of myositis. Histological analysis of her left quadriceps revealed infiltration of IgG4⁺ plasma cells as well as CD8⁺ T cells. Scattered necrotic and regenerating muscle fibers with no specific findings for IgG4-RD (storiform fibrosis and obliterator phlebitis) were typical for PM. We diagnosed her condition as PM and treated her with 40 mg/day of prednisolone that decreased levels of muscle enzymes and improved muscle weakness.

Conclusion: Our case indicated that PM could present with high serum IgG4 levels and IgG4⁺ plasma-cell infiltration, mimicking IgG4-RD. Although the mechanism of IgG4 elevation in such PM is unclear, our case highlights the necessity to recognize that high serum IgG4 levels and IgG4⁺ plasma-cell infiltration in organs are not specific for IgG4-RD.

Abbreviations: IgG4-RD = IgG4-related disease, PM = polymyositis.

Keywords: diagnosis, IgG4, IgG4-related disease, plasma cells, polymyositis

1. Introduction

Polymyositis (PM) is a type of autoimmune, inflammatory myopathy characterized by chronic inflammatory and degenerative changes in the muscles leading to muscle weakness. Mononuclear inflammatory cells infiltrating affected muscles are mainly CD8⁺ T cells rather than B and plasma cells.[1] IgG4-related disease (IgG4-RD) is a rare lymphoproliferative disorder with elevated levels of serum IgG4 and abundant IgG4⁺ plasma cell infiltration of various organs.[2,3] As IgG4-RD has been growingly recognized, cases of other diseases, such as multicentric Castleman disease,[4–6] and small vessel vasculitis,[7] presenting with those features have drawn attention because such cases could fulfill the diagnostic criteria for IgG4-RD.[5,6] We herein report the first case of PM with high serum IgG4 levels and IgG4⁺ plasma-cell infiltration of affected muscles, mimicking IgG4-RD. Our case highlights the importance of careful assessment and differential diagnosis in a patient with elevated serum IgG4 levels and tissue IgG4⁺ plasma cell infiltration. An informed consent was obtained from the patient.

2. Case presentation

A 71-year-old woman developed muscle pain and weakness in both thighs in 2014. The symptoms gradually progressed, and she was admitted to our hospital for work-up in August 2016. Physical examinations revealed normal blood pressure of 105/63 mm Hg and body temperature of 36.7°C. Manual muscle testing score of her neck flexor tendons, biceps, triceps, quadriceps, and ilopsoas muscles showed muscle weakness (neck flexor tendons: 2, biceps, triceps, quadriceps, and ilopsoas muscles; bilaterally 4). Gowers’ sign was positive. The findings of ocular, lung, cardiovascular, abdominal, other neurological, joints and skin examination were normal. She had no history of statin treatment.

Laboratory tests revealed elevated levels of serum creatinine kinase (384 IU/L, normal range: 50–170 IU/L), aldolase (6.2 IU/L, normal range: 2.7–5.9 IU/L), lactate dehydrogenase (314 IU/L, normal range: 120–220 IU/L), IgG (2603 mg/dL, normal range:...
muscle enzyme levels and improved muscle weakness. Treatment with 40mg/day of prednisolone decreased phlebitis. Figure 2H).

RD, and the affected lesion was only muscle without typical sites for IgG4-

classifying muscle fibres (Fig. 2D). Scattered necrotic and regenerating muscle fibers were all negative.

Fat-suppressed T2-weighted magnetic resonance imaging showed high intensity (Fig. 1), and needle electromyography showed spontaneous fibrillations and positive sharp waves in bilateral femoral quadriceps, suggesting the presence of myopathies. Positron-emission tomography-computed tomography demonstrated no abnormal accumulation of fluoro-2-deoxyglucose, or malignant tumor, or typical organ involvement for IgG4-RD, including lacrimal glands, salivary glands, pancreas, bile duct, kidney, aorta, and retroperitoneum.

Histological examination of her left quadriceps revealed mononuclear inflammatory cells that surrounded and invaded muscle fibers (Fig. 2A and B). Those inflammatory cells were positive for CD8 (Fig. 2C), and MHC class I antigen was extensively expressed on the surface of almost all muscle fibers (Fig. 2D). Scattered necrotic and regenerating muscle fibers as well as variations in muscle fiber size were characteristic of inflammatory myopathy (Fig. 2A and B). Infiltration of inflammatory cells at perivascular sites and perifascicular atrophy were not observed. While CD138, IgG, and IgG4 immunostaining (Fig. 2E-G) revealed that over 40% of infiltrated IgG positive plasma cells were IgG4+ cells, the important findings for IgG4-RD of storiform fibrosis and obliterator phlebitis were not found (Fig. 2H).

We diagnosed her with PM based on the Bohan and Peter classification criteria. Although she also met the 2011 comprehensive diagnostic criteria for IgG4-RD, IgG4-RD was unlikely since she had no swelling or masses in systemic organs, the affected lesion was only muscle without typical sites for IgG4-RD, and the findings of muscles showed necrotic and regenerating muscle fibers but not storiform fibrosis and obliterator phlebitis. Treatment with 40mg/day of prednisolone decreased muscle enzyme levels and improved muscle weakness.

3. Discussion

The present case demonstrated that PM could present with high serum levels of IgG4 and infiltration of IgG4+ plasma cells into the muscles, mimicking IgG4-RD. Understanding that elevation of serum IgG4 levels and IgG4+ plasma-cell infiltration of affected sites could be seen in other diseases as well as IgG4-RD is critically important for appropriate diagnosis and treatment.

Differential diagnosis of IgG4-RD includes a variety of diseases, such as autoimmune diseases, infectious diseases, and malignancies, since those diseases could present with high serum IgG4 and IgG4+ plasma-cell infiltration of affected sites; thus, the comprehensive criteria on IgG4-RD[3] and the international statement regarding management and treatment of IgG4-RD[13] have obliged the exclusion of other diseases in diagnosing patients with IgG4-RD. We reviewed cases reported to mimic IgG4-RD published between 2012 and 2016 (Table 1). All patients were diagnosed with other diseases despite the fulfillment of the comprehensive criteria on IgG4-RD.[3] Most were multicentric Castleman disease and polyangiitis, but other diseases like virus infection and malignancies were also reported. Our case is the first report of PM mimicking IgG4-RD, suggesting that such case may be rare but clinically important in respect of disease management, because the response to glucocorticoids, treatment strategy, and prognosis are different between IgG4-RD and PM.[13,18-20]

Elevated serum IgG4 levels have been reported in various diseases. Yamamoto et al[21] examined serum IgG4 levels in rheumatic and other diseases, and reported 1 patient with PM among 6 patients with high serum IgG4 levels. While T follicular helper cells induce IgG4 class-switching in IgG4-RD,[22-26] the mechanism of elevation of serum IgG4 levels in PM is unclear. Our case showed not only elevation of IgG4 levels but also elevation of IgA levels, which is not usually found in IgG4-RD, suggesting that the mechanism of IgG4 elevation in PM is different from that of IgG4-RD. We hypothesize that polyclonal elevation of immunoglobulins contributes to IgG4 elevation in PM rather than the specific skewing toward IgG4 class-switching.

Our case showing massive infiltration of plasma cells as well as CD8+ T cells at affected muscles has raised another interesting possibility in the pathogenesis of PM. Although T cells are proved important in PM, B cells and plasma cells can also be accountable.

The role of B cells and plasma cells in the pathogenesis of PM has
been shown by frequent presence of autoantibodies and hyper-
gammaglobulinemia.[28] Moreover, a local in situ differentiation of
B cells into mature plasma cells is thought to occur in the muscle
tissue of PM as clonal expansion of B cells is present in affected
muscle tissues, and significant somatic hypermutation and isotype
switching is shown by local immunoglobulin variable region
sequences.[28,29] The involvement of B cells in PM is also clinically
indicated by favorable responses to rituximab (anti-CD20
monoclonal antibody).[30,31] Taken together, our case warrants
further examinations of a role of B cells and plasma cells in PM.

Figure 2. Histopathological findings of muscle biopsy. Hematoxylin–eosin staining revealed presence of mononuclear inflammatory cells that surrounded and invaded muscle fibers and scattering of necrotic tissue and regenerating fibers as well as variations in muscle fiber size (A: low power field; B: high power field). CD8 immunostaining revealed CD8+ cell infiltration around the muscle fibers (C). MHC class I antigen was extensively expressed on the surface of almost all muscle fibers (D). CD138 staining revealed CD138+ plasma cell infiltration around the muscle fibers (E). IgG (F) and IgG4 (G) immunostaining revealed that the ratio of IgG4+/IgG+ plasma cells was over 40%. Masson-trichrome staining revealed no storiform fibrosis and obliterative phlebitis (H).
Polymyositis Our case Satis
multicentric Castleman disease 1 case Satis
6 cases Satis
Serum IgG4, mg/dL
Polymyositis
Multicentric Castleman disease
IgG4-RD, %
Serum IgG4/IgG ratio, %
Tissue IgG4+ plasma cells infiltration, %
Ref.

1 case Satis
987 22.3 55.0 [6]
930 27.8 63.0 [6]
809 34.4 52.5 [6]
3700 67.0 73.0 [6]
867 37.8 56.0 [6]
1160 24.0 51.5 [6]
389 9.5 46.5 [6]
135< Nad 40.0< [7]
1480 28.6 40.6 [6]
9 cases Satis
135< Nad 40.0< [9]
6 cases Satis
135< Nad 40.0< [9]
1 case Satis
135< Nad 40.0< [9]
1 case Satis
135< Nad 40.0< [9]
2 cases Satis
912 32.0 45.0 [14]
684 32.0 60.0 [14]
1 case Satis
637 Nad 58.0 [15]
1 case Satis
1680 80.4 40.0< [16]
1 case Satis
938 38.7 40.0< [17]

The cases which showed both high serum levels of IgG4 and IgG4+ plasma cells at affected organs were listed.

Mild to moderate dose of glucocorticoid is usually effective to IgG4-RD,[11] while a part of patients with PM are refractory,[18,19] and need intravenous immunoglobulin or other immunosuppressive agents like calcineurin inhibitors and cyclophosphamide in addition to high dose glucocorticoid.[31,32] Thus, the differentiation of PM from IgG4-RD is clinically important in the management of the disease.

4. Conclusions

We described the first case of PM that presented with elevated serum levels of IgG4 and abundant infiltration of IgG4+ plasma cells into affected sites, mimicking IgG4-RD. High serum IgG4 levels and tissue-infiltration of IgG4+ plasma cells are indicative but not specific for the diagnosis of IgG4-RD.

Uncited reference

[27].

References

[1] Venalis P, Lundberg IE. Immune mechanisms in polymyositis and dermatomyositis and potential targets for therapy. Rheumatology 2014;53:397–403.
[2] Kamisawa T, Zen Y, Pillai S, et al. IgG4-related disease. Lancet 2015;385:1460–71.
[3] Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). 2011. Mod Rheumatol 2012;22:21–30.
[4] Sasaki T, Akayama M, Kaneko Y, et al. Distinct features distinguishing IgG4-related disease from multicentric Castleman’s disease. RMD Open 2017;3:e000432.
[5] Yoshida T, Yamada K, Hara S, et al. Multicentric Castleman disease with tubulointerstitial nephritis mimicking IgG4-related disease: two case reports. Am J Surg Pathol 2016;40:495–501.
[6] Ogoshi T, Kido T, Yatera K, et al. Assessment of pathologically diagnosed patients with Castleman’s disease associated with diffuse parenchymal lung involvement using the diagnostic criteria for IgG4-related disease. Lung 2013;191:373–83.
[7] Manabe A, Igawa T, Takeuchi M, et al. Immunohistochemical analysis of IgA expression differentiates IgG4-related disease from plasma cell-type Castleman disease. Mod Mol Morphol 2017;50:34–41.
[8] Takeuchi M, Sato Y, Takata K, et al. Cutaneous multicentric Castleman’s disease mimicking IgG4-related disease. Pathol Res Pract 2012;208:746–9.
[9] Ohyama K, Koike H, Takahashi M, et al. Immunoglobulin G4-related pathologic features in inflammatory neuropathies. Neurology 2015;85:1400–7.
[10] Umehara H, Okazaki K, Kawano M, et al. How to diagnose IgG4-related disease. Ann Rheum Dis 2017;an press.
[11] Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344–7.
[12] Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). N Engl J Med 1975;292:403–7.
[13] Gianfreda D, Musetti C, Nicastro M, et al. Erdheim-Chester disease as a mimic of IgG4-related disease. Arthritis Rheumatol 2015;67:1688–99.
[14] Gianfreda D, Musetti C, Nicastro M, et al. Erdheim-Chester disease as a mimic of IgG4-related disease: a case report and a review of a single-center cohort. Medicine (Baltimore) 2016;95:e3625.
[15] Tabata T, Kamisawa T, Hara S, et al. Intraductal papillary mucinous neoplasm of the pancreas and IgG4-related disease: a coincidental association. Pancreatology 2013;13:379–83.
[16] Nakashima S, Miki K, Orta K, et al. Multicentric Castleman disease with tubulointerstitial nephritis mimicking IgG4-related disease: a case report. Medicine (Baltimore) 2005;84:231–49.
[17] Fasano S, Gordon P, Hajji R, et al. Rituximab in the treatment of inflammatory myopathies: a review. Rheumatology (Oxford) 2017;56:26–36.
[21] Yamamoto M, Tabeya T, Naishiro Y, et al. Value of serum IgG4 in the diagnosis of IgG4-related disease and in differentiation from rheumatic diseases and other diseases. Mod Rheumatol 2012;22:419–25.

[22] Akiyama M, Suzuki K, Yasuoka H, et al. Follicular helper T cells in the pathogenesis of IgG4-related disease. Rheumatology 2017;in press.

[23] Akiyama M, Suzuki K, Yamaoka K, et al. Number of circulating follicular helper 2 T cells correlates with IgG4 and interleukin-4 levels and plasmablast numbers in IgG4-related disease. Arthritis Rheumatol 2015;67:2476–81.

[24] Akiyama M, Yasuoka H, Yamaoka K, et al. Enhanced IgG4 production by follicular helper 2 T cells and the involvement of follicular helper 1 T cells in the pathogenesis of IgG4-related disease. Arthritis Res Ther 2016;18:167.

[25] Akiyama M, Kaneko Y, Yamaoka K, et al. Subclinical labial salivary gland involvement in IgG4-related disease affected with vital organs. Clin Exp Rheumatol 2015;33:949–50.

[26] Akiyama M, Suzuki K, Kassai Y, et al. Resolution of elevated circulating regulatory T cells by corticosteroids in patients with IgG4-related dacryoadenitis and salivaryadenitis. Int J Rheum Dis 2016;19:430–2.

[27] Yuseff MI, Pierobon P, Reversat A, et al. How B cells capture, process and present antigens: a crucial role for cell polarity. Nat Rev Immunol 2013;13:475–86.

[28] Grundtman C, Malmström V, Lundberg IE. Immune mechanisms in the pathogenesis of idiopathic inflammatory myopathies. Arthritis Res Ther 2007;9:208.

[29] Bradshaw EM, Orihuela A, McArdel SL, et al. A local antigen-driven humoral response is present in the inflammatory myopathies. J Immunol 2007;178:547–56.

[30] Nalotto L, Iaccarino L, Zen M, et al. Rituximab in refractory idiopathic inflammatory myopathies and antisynthetase syndrome: personal experience and review of the literature. Immunol Res 2013;56:362–70.

[31] Cherin P, Pelletier S, Teixeira A, et al. Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. Arthritis Rheum 2002;46:467–74.

[32] Moghadam-Kia S, Aggarwal R, Oddis CV. Treatment of inflammatory myopathy: emerging therapies and therapeutic targets. Expert Rev Clin Immunol 2015;11:1263–73.