

IgG4-related Sclerosing Pachymeningitis

A Previously Unrecognized Form of Central Nervous System Involvement in IgG4-related Sclerosing Disease

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Abstract: IgG4-related sclerosing disease is a distinctive mass-forming lesion with frequent systemic involvement, most frequently the pancreas, salivary glands, and lacrimal glands. This report describes a case manifesting with a previously unrecognized form of central nervous system involvement. The 37-year-old man presented with signs and symptoms of spinal cord compression at the thoracic level 9. Magnetic resonance imaging revealed an elongated dural mass extending from the fifth to tenth thoracic vertebra. Laminectomy and excision of the mass revealed dura expanded by a dense lymphoplasmacytic infiltrate accompanied by stromal fibrosis and phlebitis. IgG4+ plasma cells were increased and the proportion of IgG4+/IgG+ plasma cells was 85%. The patient also had a 1-year history of bilateral submandibular swelling due to chronic sialadenitis. Thus, IgG4-related sclerosing pachymeningitis represents a new member of the IgG4-related sclerosing disease family affecting the central nervous system. It seems that at least a proportion of cases described in the literature as idiopathic hypertrophic pachymeningitis belong to this disease, especially as some patients have other clinical manifestations compatible with IgG4-related sclerosing disease, such as cholangitis and orbital pseudotumor.

Key Words: IgG4-related sclerosing disease, IgG4-related pachymeningitis, spinal cord compression, central nervous system, idiopathic hypertrophic pachymeningitis

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IgG4-related sclerosing disease is a syndrome characterized by tumor-like involvement of exocrine glands or other extranodal sites by lymphoplasmacytic infiltration and sclerosis, accompanied by increased IgG4+ plasma cells in the tissues and elevated IgG4 titer in the serum, and often showing good response to steroid therapy.^{3–6,9,10,15,19} Central nervous system involvement

has not been described, except for 5 cases of hypophysitis presenting as mass lesion with optic nerve compression and hypopituitarism in 1 and hypopituitarism or central diabetes insipidus as part of multiorgan involvement by IgG4-related sclerosing disease in the other 4.^{13,22–25} We herein describe a case of mass-forming inflammatory lesion of the dura mater presenting clinically with spinal cord compression, a feature not previously recognized in IgG4-related sclerosing disease.

CASE REPORT

A 37-year-old man presented with bilateral lower limb weakness, decreased sensation, and numbness associated with unsteady gait for 2 weeks. Physical examination revealed a sensory level at thoracic level 9, and extensor plantar reflexes and ankle clonus were elicited bilaterally. Magnetic resonance imaging with contrast revealed an extradural spindle-shaped lesion over the dorsal aspect of the spinal canal extending from the fifth to tenth thoracic vertebra (Fig. 1). Laboratory investigations were essentially normal and serum autoimmune markers including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, antinuclear antibodies, C3, C4, antismooth muscle antibodies, antineutrophilic cytoplasmic antibody, and antiextractable nuclear antigen were all within the normal range. Preoperative serum IgG4 level was not available. Emergency operation showed a firm yellowish mass arising from the dorsal aspect of the dura from the fifth to tenth thoracic vertebra, measuring 14 cm long and 8 mm in largest diameter. With a frozen section diagnosis of chronic inflammation, laminectomy and excision of the mass was performed.

The patient actually had a 1-year history of bilateral submandibular gland swelling. Fine needle aspiration yielded scanty lymphoid cells and ductal cells, compatible with chronic sialadenitis. There were no complaints of dry mouth.

PATHOLOGIC FINDINGS

Received for pathologic examination were multiple fragments of firm tissue. Microscopic examination revealed dura expanded by a patchy dense infiltrate of plasma cells and small lymphocytes, accompanied by prominent stromal sclerosis and many medium-sized blood vessels. The sclerosis took the form of thick collagen fibers or homogenized fibrous tissue. Many reactive lymphoid follicles were present (Fig. 2). Small numbers of eosinophils and some aggregates of neutrophils were also detected. Phlebitis was readily seen (Fig. 2C), which could be highlighted by elastic van

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FIGURE 1. The sagittal T2-weighted magnetic resonance image showed a hyperintense extradural spindle-shaped lesion over the dorsal aspect of the spinal canal extending from the fifth to tenth thoracic vertebra. The lesion showed homogeneous gadolinium enhancement.

Gieson stain, featuring transmural lymphoplasmacytic infiltrate and fragmentation of elastic lamina. No neural tissues were identified in the specimen. Grocott and Warthin-Starry stains did not reveal microorganisms, and polymerase chain reaction for *Mycobacterium tuberculosis* was negative.

Immunohistochemical staining revealed many CD3-positive T-lymphocytes in the inflammatory infiltrates, whereas CD20-positive B-cells were largely confined to the follicles. The plasma cells were polytypic. The number of IgG4+ plasma cells was increased up to 310/high power field, constituting 70% of all IgG+ plasma cells (Figs. 2D, E).

DISCUSSION

IgG4-related sclerosing disease has emerged as a distinctive clinicopathologic entity usually with evidence of systemic involvement. Although the initial characterization of this disease started with autoimmune pancreatitis, ever-growing numbers of extrapancreatic sites of involvement have been reported, such as bile duct, salivary gland, lacrimal gland, lung, retroperitoneum, breast, prostate, lymph node, and soft tissue.^{3,6,7,14,26} This report describes a case of IgG4-related sclerosing disease presenting as an elongated epidural mass causing spinal cord compression which can be aptly labeled as “IgG4-related sclerosing pachymeningitis.” The histologic features (including phlebitis) and the high numbers of IgG4+ plasma cells with an increased proportion of IgG4+/IgG+ cells are characteristic of this disease entity. The otherwise unexplained bilateral submandibular gland swelling due to chronic sialadenitis is also a well-known manifestation of IgG4-related sclerosing disease.¹⁵

The presence of dense plasma cell infiltrate can raise the possibility of Rosai-Dorfman disease, which is excluded by the lack of the distinctive large histiocytes on morphologic examination and S100 protein immunostaining. The lesion differs from inflammatory pseudotumor (inflammatory myofibroblastic tumor) in that there is no significant spindle cell (myofibroblasts) proliferation in the stroma.

This case in fact fulfills the clinicopathologic features of hypertrophic pachymeningitis, which is a rare fibroinflammatory lesion causing thickening of the dura in the cranium and/or spinal canal, and characterized histologically by dense fibrosis and lymphoplasmacytic infiltrates.^{8,16,21} Early reports generally attributed syphilis^{11,12} or tuberculosis¹⁸ as the causative agents, but more recently reported cases were mostly idiopathic. The incidence of idiopathic hypertrophic pachymeningitis has apparently increased since the advent of imaging studies.²⁰ The affected patients are usually elderly men presenting with radiculomyelopathy, headache, or cranial nerve palsies depending on the site of involvement.^{2,16,21} In the literature, some cases of idiopathic hypertrophic pachymeningitis have been associated with other fibrosclerosing diseases, such as sclerosing cholangitis, episcleritis, orbital pseudotumor, Riedel thyroiditis, testicular fibrosis, mediastinal fibrosis, and subcutaneous fibrosis.^{1,17} Autoimmune markers are frequently raised, and the clinical response to steroid is favorable.¹⁶ These patterns of systemic involvement and clinicopathologic findings are practically superimposable on those of the IgG4-related sclerosing disease. Thus, in conjunction with the current case demonstrating an IgG4-related etiology, we believe that at least a proportion of cases of idiopathic hypertrophic pachymeningitis represent a component of IgG4-related sclerosing disease. Further immunohistochemical studies on archival cases may help to clarify this issue.

In summary, IgG4-related sclerosing pachymeningitis represents yet another member of the expanding family of IgG4-related sclerosing diseases. To the best of our knowledge, this is the first report of dural involvement

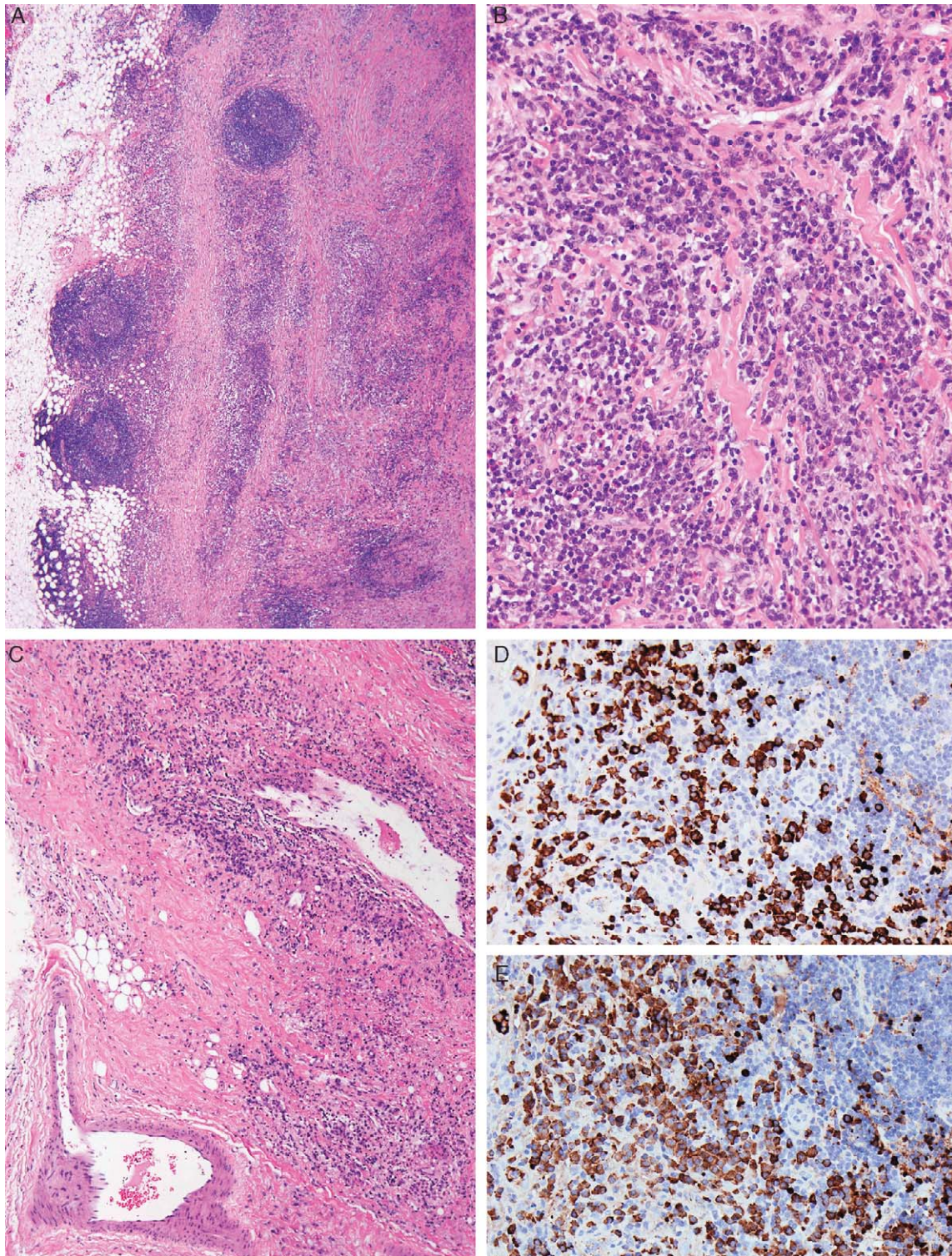


FIGURE 2. A, In a fibrotic stroma composed of lamellated collagen fibers, there are patchy dense infiltrates of lymphoid cells with reactive lymphoid follicle formation. B, The lymphoid infiltrate comprises a mixture of mature plasma cells and small lymphocytes. C, Phlebitis is evident in the upper field—the vein shows transmural infiltration by lymphocytes and plasma cells. An adjacent artery (lower field) is spared of the inflammation. D, Immunostaining reveals numerous IgG4+ plasma cells. E, A corresponding immunostaining for IgG. In this field the IgG4+ plasma cells constitute 70% of all IgG+ plasma cells.

of the central nervous system. In view of the strategic anatomic localization of the involved tissue, prompt diagnosis and steroid treatment with or without surgery may be considered to avoid neural damage.

REFERENCES

- Berger JR, Snodgrass S, Glaser J, et al. Multifocal fibrosclerosis with hypertrophic intracranial pachymeningitis. *Neurology*. 1989;39:1345–1349.
- Botella C, Orozco M, Navarro J, et al. Idiopathic chronic hypertrophic craniocervical pachymeningitis: case report. *Neurosurgery*. 1994;35:1144–1149.
- Cheuk W, Chan JK. Autoimmune pancreatitis: prototype of IgG4-related sclerosing disease. *Adv Anat Pathol*. 2007;14:235–236.
- Cheuk W, Yuen HK, Chan JK. Chronic sclerosing dacryoadenitis: part of the spectrum of IgG4-related Sclerosing disease? *Am J Surg Pathol*. 2007;31:643–645.
- Cheuk W, Yuen HK, Chan ACL, et al. Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. *Am J Surg Pathol*. 2008;32:1159–1167.
- Cheuk W, Yuen HK, Chu SY, et al. Lymphadenopathy of IgG4-related sclerosing disease. *Am J Surg Pathol*. 2008;32:671–681.
- Cheuk W, Chan ACL, Lam WL, et al. IgG4-related sclerosing mastitis: description of a new member of the IgG4-related sclerosing diseases. *Am J Surg Pathol*. 2009. In press.
- Guidetti B, La Torre E. Hypertrophic spinal pachymeningitis. *J Neurosurg*. 1967;26:496–503.
- Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med*. 2001;344:732–738.
- Hamano H, Arakura N, Muraki T, et al. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. *J Gastroenterol*. 2006;41:1197–1205.
- Hassin G. Histogenesis of cerebral hypertrophic pachymeningitis. *Am J Syphilis*. 1918;2:715.
- Hassin G, Zeitlin H. Syphilitic cerebral hypertrophic pachymeningitis: clinicopathologic studies in a case. *Arch Neurol Psychiatry*. 1940;43:362–371.
- Isaka Y, Yoshioka K, Nishio M, et al. A case of IgG4-related multifocal fibrosclerosis complicated by central diabetes insipidus. *Endocr J*. 2008;55:723–728.
- Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol*. 2008;14:3948–3955.
- Kitagawa S, Zen Y, Harada K, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). *Am J Surg Pathol*. 2005;29:783–791.
- Kupersmith MJ, Martin V, Heller G, et al. Idiopathic hypertrophic pachymeningitis. *Neurology*. 2004;62:686–694.
- Levine MR, Kaye L, Mair S, et al. Multifocal fibrosclerosis. Report of a case of bilateral idiopathic sclerosing pseudotumor and retroperitoneal fibrosis. *Arch Ophthalmol*. 1993;111:841–843.
- Naffziger H, Stern W. Chronic pachymeningitis. *Arch Neurol Psychiatry*. 1949;62:383–411.
- Okazaki K, Uchida K, Ohana M, et al. Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response. *Gastroenterology*. 2000;118:573–581.
- Pai S, Welsh CT, Patel S, et al. Idiopathic hypertrophic spinal pachymeningitis: report of two cases with typical MR imaging findings. *AJNR Am J Neuroradiol*. 2007;28:590–592.
- Riku S, Kato S. Idiopathic hypertrophic pachymeningitis. *Neuropathology*. 2003;23:335–344.
- Tanabe T, Tsushima K, Yasuo M, et al. IgG4-associated multifocal systemic fibrosis complicating sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic involvement. *Intern Med*. 2006;45:1243–1247.
- van der Vliet HJ, Perenboom RM. Multiple pseudotumors in IgG4-associated multifocal systemic fibrosis. *Ann Intern Med*. 2004;141:896–897.
- Wong S, Lam WY, Wong WK, et al. Hypophysitis presented as inflammatory pseudotumor in immunoglobulin G4-related systemic disease. *Hum Pathol*. 2007;38:1720–1723.
- Yamamoto M, Takahashi H, Ohara M, et al. A case of Mikulicz's disease (IgG4-related plasmacytic disease) complicated by autoimmune hypophysitis. *Scand J Rheumatol*. 2006;35:410–411.
- Yamashita K, Haga H, Kobashi Y, et al. Lung involvement in IgG4-related lymphoplasmacytic vasculitis and interstitial fibrosis: report of 3 cases and review of the literature. *Am J Surg Pathol*. 2008;32:1620–1626.