

IgG4-Related Disease and Hypertrophic Pachymeningitis

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Abstract: Hypertrophic pachymeningitis (HP) is an inflammatory condition in which the dura mater of the cranium or spine becomes thickened, leading to symptoms that result from mass effect, nerve compression, or vascular compromise. The differential diagnosis of HP includes immune-mediated conditions such as rheumatoid arthritis and vasculitis, malignancies, and infections. Many times, no diagnosis is reached; in such cases, the disease has been described as idiopathic HP. IgG4-related disease (IgG4-RD) is a recently described inflammatory condition known to cause tumefactive lesions at myriad anatomical locations. Both IgG4-RD and idiopathic HP share similar demographics, histopathology, and natural history. We hypothesized that IgG4-RD is a common cause of idiopathic HP.

To investigate this hypothesis, we identified all pathology specimens diagnosed as noninfectious HP during 25 years at our institution. Fourteen cases had stained slides and paraffin blocks to permit review of the original hematoxylin and eosin stained slides as well as immunostaining of cell blocks. Recently published consensus guidelines describing characteristic histopathology and the necessary quantity of IgG4+ plasma cell infiltrate were used to diagnose IgG4-RD.

Four cases (66.6%) that had been regarded previously as representing idiopathic HP were diagnosed as IgG4-RD; of all the reviewed cases, IgG4-RD represented 29% of cases. Of the remaining cases, 3 cases were associated with granulomatosis with polyangiitis (GPA), 2 with lymphoma, and 1 each with rheumatoid arthritis, giant cell arteritis, and sarcoidosis. Two of the cases could not be diagnosed more precisely and were classified as undifferentiated HP. Clinical history, serologic tests, cerebrospinal fluid studies, and radiology alone could not identify the cause of HP. Rather, biopsy with histopathology and immunostaining was necessary to reach an accurate diagnosis. Significant IgG4+ plasma cell infiltrates were observed in rheumatoid arthritis, granulomatosis with polyangiitis, and lymphoma, underscoring the importance of histopathology in making the diagnosis of IgG4-RD.

This case series demonstrates that IgG4-RD may be the most common etiology of noninfectious HP and highlights the necessity of biopsy for accurate diagnosis.

(*Medicine* 2013;92: 206–216)

Abbreviations: ANCA = antineutrophil cytoplasmic antibodies, CNS = central nervous system, CSF = cerebrospinal fluid, CT = computed tomography, GPA = granulomatosis with polyangiitis, HP = hypertrophic pachymeningitis, HPF = high-power field, IgG4-RD = IgG4-related disease, MRI = magnetic resonance imaging, WBC = white blood cell.

INTRODUCTION

Hypertrophic pachymeningitis (HP) refers to inflammation leading to a localized or diffuse thickening of the cranial or spinal cord dura mater. Patients usually present with symptoms related to mass effect or focal deficits caused by the compression of blood vessels or nerves.^{2,5} The differential diagnosis for HP is broad, including vasculitic disorders (for example, granulomatosis with polyangiitis [formerly Wegener granulomatosis; herein termed GPA], giant cell arteritis, and Behçet disease); other immune-mediated conditions (for example, rheumatoid arthritis, sarcoidosis); malignancies (for example, lymphoma); and infections (such as, tuberculosis). The evaluation of HP cases involves laboratory investigations of both blood and cerebrospinal fluid (CSF) samples, cross-sectional imaging studies, and pachymeningeal biopsies.

The precise diagnosis in pachymeningitis often remains elusive despite these thorough investigations. Cases in which the pachymeningitis has no known etiology are termed “idiopathic” HP.^{1,12,14,25,26,29,35,37,41,45} To our knowledge, the first case of idiopathic HP was described in 1869 by Charcot and Joffroy.⁷ However, many idiopathic HP cases share a common histology—namely, a lymphoplasmacytic infiltrate with fibrosis—and some cases have been associated with inflammatory lesions elsewhere, including the orbit and thyroid gland.^{2,4,13,25,30,49,50} Reviews of idiopathic HP suggest that men are affected more commonly than women by this condition and that patients typically present in the sixth or seventh decades of life.²⁵

The histopathologic features described for idiopathic HP, the frequency and type of organ involvement beyond the pachymeninges, and the demographic characteristics of idiopathic HP have many similarities with an emerging inflammatory condition known as IgG4-related disease (IgG4-RD).⁴³ Indeed, several case reports and a case series have implicated IgG4-RD as a cause of HP,^{6,24,28,36} but the relative frequency of IgG4-RD as the cause of pachymeningitis remains uncertain. We hypothesized that IgG4-RD accounts for a substantial subset of patients with immune-mediated HP, just as IgG4-RD is now known to cause a significant proportion of cases of orbital inflammatory disease,⁴⁹ lymphoplasmacytic aortitis,^{15,42} retroperitoneal fibrosis,¹⁸ and several other conditions previously considered to be of obscure etiology.^{21,40}

To investigate this hypothesis, we examined 14 cases of pachymeningitis evaluated at our institution, 6 of which had been attributed previously to idiopathic HP. We based the diagnosis of IgG4-related pachymeningitis on recently published (2012) consensus guidelines.¹⁰

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Drs. Wallace and MN Carruthers contributed equally to this manuscript. Figures 2 and 3 can be viewed in color online at <http://www.md-journal.com>. Financial support and conflicts of interest: Dr. Stone reports financial support for work outside this study from Genentech and Roche (consulting fees in the area of systemic vasculitis) and a grant/grant pending to his institution from Genentech (clinical trial to investigate the role of rituximab in the treatment of IgG4-related disease). The other authors have no funding or conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0b013e31829cce35

METHODS

We searched the pathology database at the Massachusetts General Hospital to identify all pathology specimens identified as HP over a 25-year time span. We identified 15 cases of HP for which the original pathology slides were available for review; 1 case was excluded because a paraffin block was unavailable. Hematoxylin and eosin stained slides were reviewed in a blinded manner by 1 of the authors (VD) to determine the histopathologic features. Paraffin blocks were available for all cases and were stained by immunohistochemistry for IgG4 and IgG. Immunohistochemistry was performed using antibodies to IgG4 (Zymed; 1:200 dilution) and IgG (Dako; 1:3000 dilution). Counting was performed with the assessors (SS, VD) blinded to the patients' clinical details. For each case, the number of plasma cells staining for IgG4 was assessed in 3 non-overlapping high-power fields (HPFs; magnification of $\times 400$). The fields with the highest degree of IgG4 reactivity were selected for counting.¹⁰ The number of IgG4+ plasma cells was then divided by the total number of IgG+ plasma cells in these fields to determine the IgG4+/IgG+ ratio. We thereby determined the fraction of plasma cells that stained for IgG4.

The diagnosis of IgG4-RD hinges on the presence of both specific histopathologic features and an increased number of IgG4+ plasma cells (or IgG4+/IgG+ ratio) in the affected tissue, in conjunction with close clinicopathologic correlation.¹⁰ The major histopathologic features include a dense lymphoplasmacytic infiltrate, fibrosis that has a storiform pattern in focal areas (if not diffusely), and obliterative phlebitis. At least 2 of these 3 features must be present to diagnose IgG4-RD.¹⁰ Nonobliterative phlebitis and mild to moderate degrees of tissue eosinophilia, both considered to be minor pathologic features, may also be present.¹⁰ In addition, a cutoff of >10 IgG4+ plasma cells per HPF was used, and an IgG4+/IgG+ ratio of at least 0.40 was considered essential to the diagnosis.¹⁰

The histopathologic basis of the diagnosis of GPA includes the following findings: 1) granulomatous inflammation of the arteries, veins, and capillaries; 2) necrosis either within microabscesses or in large, "geographic" regions; and 3) granulomatous inflammation indicated by palisading granulomas, giant cells, and/or poorly formed granulomas.⁴⁷ Rheumatoid arthritis was established by identifying rheumatoid nodules within the meninges in the setting of a clinical diagnosis of rheumatoid arthritis.¹ The diagnosis of neurosarcoidosis was based on the finding of noncaseating granulomas and the exclusion of infections through appropriate cultures.³³ The diagnosis of giant cell arteritis was predicated on both a temporal artery biopsy and findings of granulomatous inflammation compatible with that condition within a dural blood vessel (and confirmation in a temporal artery biopsy). Lymphoma was diagnosed according to the World Health Organization classification of non-Hodgkin's lymphoma, based on histology, immunohistochemistry or flow cytometry, a calculated proliferation index, and genetic studies.

All cases underwent Gram stain, acid-fast bacilli, and Grocott methenamine silver or Warthin-Starry stains for fungal organisms. If granulomas were present, additional stains including periodic acid-Schiff (PAS), Brown Hopps, and Giemsa were performed. The Warthin-Starry stain for syphilis was done in 2 cases due to clinical suspicion. Details of any additional infectious workup are included in the individual case summaries.

RESULTS

Among the 14 cases of HP identified, there were 4 cases caused by IgG4-RD, 3 associated with GPA, 2 with lymphoma, and 1 each with rheumatoid arthritis, giant cell arteritis, and sarcoidosis. Two of the cases could not be diagnosed more precisely and were classified as undifferentiated HP. (Four cases have been previously described in published case reports; see Table 1.) We

TABLE 1. Clinical Features of Pachymeningitis Patients

Case	Diagnosis*	Site	Age (yr)	Sex	Symptom	CSF Cells (mm ³)	CSF Lymph (%)	CSF Protein†(mg/dL)
1	IgG4-RD ³⁸	Intracranial dura	50	F	Seizures	NP	NP	NP
2	IgG4-RD	Intracranial dura	52	F	Headache	112	94	135
3	IgG4-RD	Intracranial dura	39	M	Headache, arm numbness	4	88	22
4	IgG4-RD	L5 nerve root dura	32	M	Weakness	NP	NP	NP
5	GPA	T2–T8 dura	59	F	Sensory abnormalities, urinary retention	NP	NP	NP
6	GPA	Intracranial dura	75	F	Gait instability	86	96	57
7	GPA	Intracranial dura	55	M	Painful diplopia	NP	NP	NP
8	Rheumatoid arthritis ⁹	Intracranial dura	58	F	Ataxia, numbness, visual loss	6	78	19
9	Giant cell arteritis ³	Intracranial dura	59	M	Central DI	NP	NP	NP
10	Neurosarcoidosis	Intracranial dura	67	M	Nausea, vomiting, ataxia	378	NP	198
11	MALT lymphoma	Intracranial dura	52	M	Headache, dizziness	NP	NP	NP
12	Non-Hodgkin lymphoma	Intracranial dura	61	F	Cranial nerve III palsy	23	81	27
13	Undifferentiated ⁵⁰	Intracranial dura	44	F	Headaches, thrombosis	34	86	46.9
14	Undifferentiated	Intracranial dura	75	M	FUO, gait instability, eye pain	3	31	39

Abbreviations: DI = diabetes insipidus, FUO = fever of unknown origin, MALT = mucosa-associated lymphoid tissue, NP = not performed.

*Cases 1, 8, 9, and 13 have been previously described in published case reports (references noted here).

†Normal CSF protein: 10–44 mg/dL.

describe 7 of these cases in detail below, with an emphasis on the IgG4-RD cases, to underscore their characteristic features.

Illustrative Case Summaries

Case 1: IgG4-RD

A 50-year-old woman with a history of Henoch-Schönlein purpura in childhood and Tolosa-Hunt syndrome at age 36 years experienced a focal left-sided seizure 6 years before presentation to our institution. Over the next several months, recurrent seizures and difficulty with ambulation prompted a magnetic resonance imaging (MRI) study of the brain that revealed multiple meningeal masses (Figure 1A). She was treated with dexamethasone and diphenylhydantoin and subsequently underwent elective resection of the masses. A biopsy from the meningeal lesions revealed a fibroinflammatory lesion with a lymphoplasmacytic infiltrate. Granulomas and necrosis were absent. Stains for mycobacterial and fungal organisms were negative. The diagnosis of idiopathic HP was rendered originally.

Over the next several years, the patient's seizures were suppressed effectively and her glucocorticoid and anticonvulsant therapies were discontinued. A routine follow-up MRI several years after the patient's initial presentation revealed worsening nodularity and enhancement of the pachymeninges. She was started on prednisone (60 mg daily) and methotrexate (25 mg weekly). A subsequent MRI showed improvement in the size of the nodularity and degree of enhancement. Prednisone was tapered to discontinuation.

The patient's seizures recurred months later and an MRI revealed progression of the disease. Prednisone (50 mg daily) was resumed and the pathology from the original resection was reviewed. This time, IgG4-staining—not performed originally—revealed 45 IgG4+ cells/HPF and an IgG4+/IgG+ ratio of 90%. In the setting of storiform fibrosis and a diffuse IgG4+ plasma cell-enriched lymphoplasmacytic infiltrate, the patient was diagnosed with IgG4-RD. The patient was treated with rituximab (1 g × 2 doses) and has been off of prednisone for 8 months following the second infusion. Six months after her first rituximab infusion, the patient was treated again with rituximab (1 g × 2 doses) without a need to resume prednisone.

Case 2: IgG4-RD

A 52-year-old woman with a history of polysubstance abuse presented to an outside hospital with difficulty articulating speech. She also experienced right-sided tinnitus, hearing loss, and difficulty with balance. Over the next several months, she was treated with several courses of antibiotics for similar symptoms. One year after her initial presentation, the patient developed occipital headaches associated with photophobia, nausea, and vomiting, followed by recurrent dysarthria, right facial weakness and numbness, dysphagia, and difficulty with balance. Neurologic examination revealed deficits involving cranial nerves VII, VIII, X, and XII on the right.

A lumbar puncture revealed a lymphocytic pleocytosis (CSF: 112 white blood cells [WBCs]/mm³, 94% lymphocytes, and total

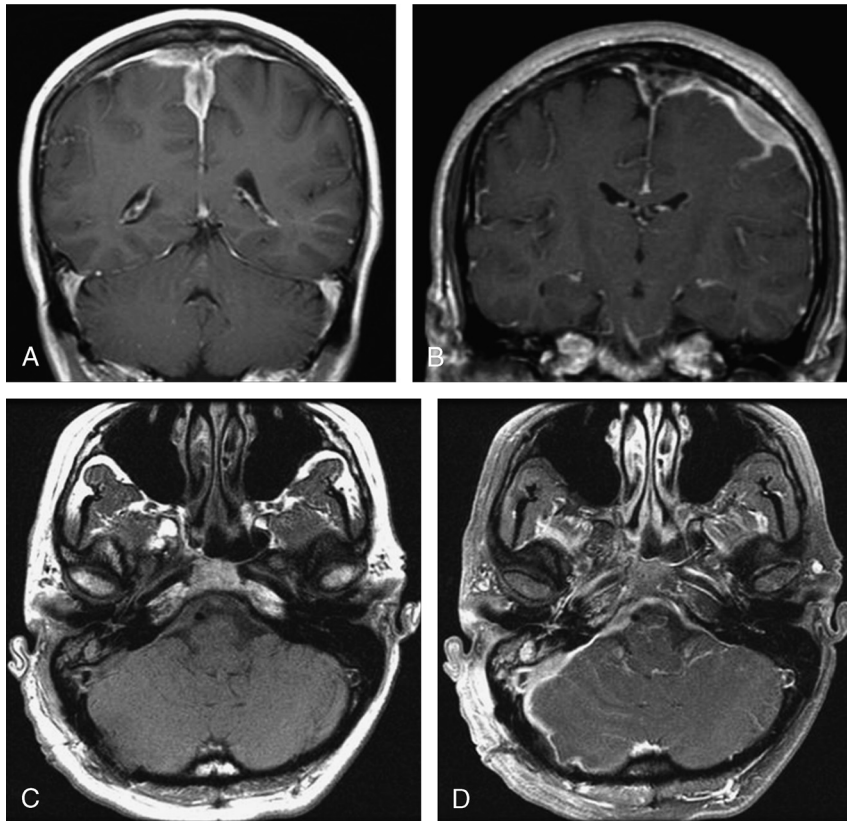


FIGURE 1. MRI findings of IgG4-related pachymeningitis. A. (Case 1) Coronal T1 postgadolinium image with lobulated expansile lesions of the falx and parafalcine dura with areas of mass effect on the brain. B. (Case 3) Coronal T1 postgadolinium image shows left cerebral convexity lepto- and pachymeningitis. C and D. (Case 2) Axial T1 pre- and postgadolinium images disclosing right-sided pachymeningitis involving the tentorium and posterior fossa with areas of right cerebellar leptomeningeal enhancement adjacent to right mastoid air cells enhancement.

protein 135 mg/dL [normal, 10–44 mg/dL]. An MRI revealed pachymeningitis and enhancement of cranial nerves VII and VIII as well as right-sided mastoiditis (Figure 1C and D). The patient was treated with antibiotics without improvement in symptoms. Dural biopsy revealed a dense lymphoplasmacytic infiltrate and storiform fibrosis with a few poorly formed granulomas but no necrosis (Figure 2A and B). Stains for mycobacterial and fungal organisms were negative. A focus of phlebitis was identified.

Several months later, the patient was readmitted with increasing fatigue, headache, left-sided hearing loss, facial numbness, and droop. Her dysarthria was worse compared with baseline and her tongue deviated to the left. There was decreased high frequency hearing in the left ear. Cross-sectional brain imaging revealed continued resolution of the right mastoiditis and no new findings. Over the next several years, the patient's headaches were treated with various combinations of pregabalin, gabapentin, nortriptyline, nonsteroidal antiinflammatory drugs, and narcotics.

Several years later, worsening of the chronic daily headaches led to an emergency department presentation. A lumbar puncture again revealed a lymphocytic pleocytosis (CSF WBC count, 21 cells/mm³ [96% lymphocytes]) and a CSF protein concentration of 71.6 mg/dL (normal, 10–44 mg/dL). An MRI showed pachymeningeal thickening and enhancement, predominantly over the posterior portion of the right hemisphere and extending to the right skull base. Immunohistochemical staining of the original dural biopsy revealed 161 IgG4+ plasma cells/HPF and an IgG4+/IgG+ ratio of 51%. Review of her mastoid biopsy from 1 year earlier was also consistent with IgG4-RD, with storiform fibrosis and a dense lymphoplasmacytic infiltrate. There were 35 IgG4+ plasma cells per HPF in the mastoid biopsy, and an IgG4+/IgG+ ratio of 35%. She was diagnosed with IgG4-RD and started on prednisone, but tapering of this medication resulted in a worsening of her baseline headache while she

was still on 40 mg/d. She was therefore treated with rituximab (1 g intravenously \times 2 doses). The patient has been headache free and off of prednisone for 11 months subsequent to B-cell depletion. A follow-up MRI 3 months after B-cell depletion showed resolving pachymeningitis.

Case 3: IgG4-RD

A previously healthy 39-year-old man from Laos presented to a hospital with a seizure in the setting of 2 months of left retrobulbar headaches. He was started on diphenylhydantoin and discharged home. His headaches persisted after discharge and he developed 2 weeks of numbness in the right arm and torso, prompting admission to our hospital. An MRI revealed 2 enhancing, left-sided, extra-axial lesions, 1 (5.8 \times 5.8 \times 1 cm) in the frontoparietal region and the other (1.5 \times 1.5 \times 1.7 cm) in the occipital region (Figure 1B). A lumbar puncture demonstrated 4 WBCs/mm³ (88% lymphocytes) and a CSF protein concentration of 22 mg/dL (normal, 10–44 mg/dL). A dural biopsy was performed and stains and cultures for acid-fast bacilli, fungi, bacteria, and parasites were negative; flow cytometry was normal. The diagnosis of idiopathic HP was made at that time, based on a lymphoplasmacytic infiltrate without evidence to suggest an alternative diagnosis. No immunosuppressive medications were administered. Follow-up MRIs at 3, 6, and 18 months showed improvement of both lesions without any intervention other than continued anticonvulsants. The patient was subsequently lost to follow-up.

On review of the original dural biopsy, he was found to have a lymphoplasmacytic infiltrate with storiform fibrosis along with occasional histiocytes, neutrophils, and eosinophils but no phlebitis. There were 98 IgG4+ plasma cells/HPF and an IgG4+/IgG+ ratio of 70% (Figure 2C).

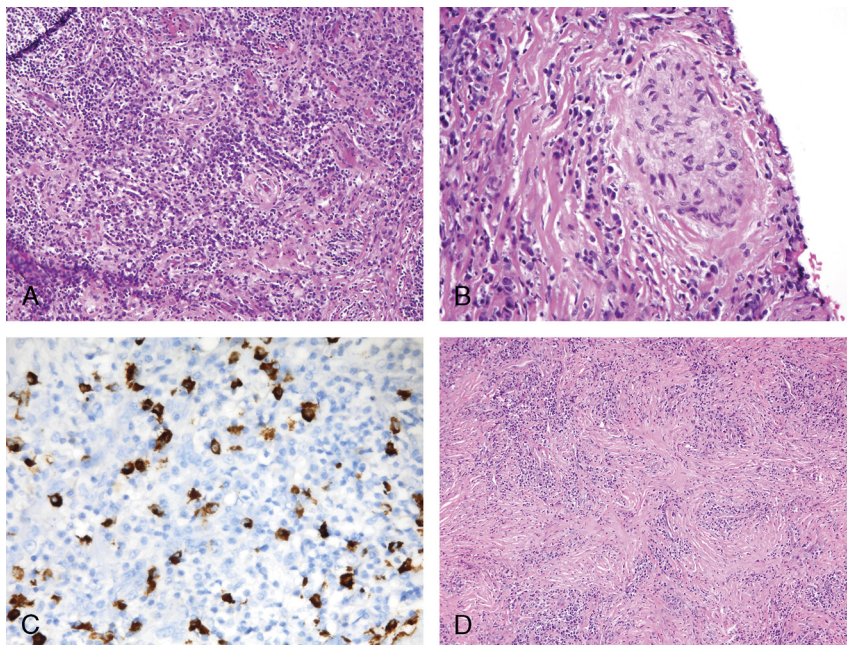


FIGURE 2. Histopathologic findings in IgG4-related pachymeningitis. A. (Case 2) The tumoral lesion is composed predominantly of fibrosis, lymphocytes, and plasma cells. B. (Case 2) Microgranuloma composed of epithelioid histiocytes. C. (Case 3) An IgG4 immunoperoxidase stain shows numerous IgG4+ plasma cells throughout the lesion. D. Higher power image shows storiform-type fibrosis. [This figure can be viewed in color online at <http://www.md-journal.com>.]

Case 4: IgG4-RD

A 32-year-old man presented with pain, sensory changes, and weakness of the dorsum of the right foot and was found to have a mass involving the right L5 nerve root. He was admitted for decompression of the mass, which was expected to be either a neurofibroma or schwannoma. At hemilaminectomy, he was found to have a thickened dura, biopsy of which revealed a lymphoplasmacytic infiltrate accompanied by eosinophils and occasional macrophages. There were no granulomas. He was thought to have idiopathic HP, recuperated well from the procedure, and had no further care in our hospital system following discharge. Re-examination of the surgical sample demonstrated a lymphoplasmacytic infiltrate, storiform fibrosis, and eosinophils. There were approximately 10 IgG4+ plasma cells/HPF, and an IgG4+/IgG+ ratio of 35%.

Case 6: Granulomatosis With Polyangiitis (GPA) (Wegener)

A 75-year-old woman developed a 6-month history of memory loss, chronic daily headaches, and progressive difficulty with her activities of daily living. She presented to medical attention following a fall and was found to have global weakness. An MRI of the brain revealed hydrocephalus and enhancement of the cerebellum tentorium. Lumbar puncture revealed a lymphocytic pleocytosis (CSF WBC count, 86 cells/mm³ [96% lymphocytes]) and an elevated CSF protein (57 mg/dL [normal, 10–44 mg/dL]). Flow cytometry studies indicated that the pleocytosis was polyclonal. Bacterial, fungal, and acid-fast bacilli cultures, as well as assays for antibodies to spirochetal pathogens (*Treponema pallidum* and *Borrelia burgdorferi*), and *Histoplasma capsulatum* were all negative. A computed tomography (CT) scan of the chest, abdomen, and pelvis was unremarkable. Progression of the symptoms required a ventriculostomy as well as biopsy of the cerebellum and the overlying tentorium. The dural biopsy showed

numerous multinucleated giant cells and arteritis, characteristic of GPA (Figure 3A). Special stains and cultures for acid-fast organisms and fungi were negative. An enzyme immunoassay for antineutrophil cytoplasmic antibodies (ANCA) was positive at 138 units (normal, <2.8 units), and a diagnosis of GPA was made. Review of the dural biopsy specimen and immunostaining for IgG4 for the purpose of this study showed storiform fibrosis but no IgG4+ plasma cells. The patient was treated with prednisone and cyclophosphamide.

Case 10: Sarcoidosis

A 67-year-old man with an unremarkable medical history presented with 2 years of difficulty with mentation and new decreasing visual acuity bilaterally. His vision loss was described as “a variable haze” over his entire visual field. One and a half years before his presentation, he had developed rapid complete hearing loss in the left ear. An MRI at an outside hospital at that time reportedly demonstrated meningeal enhancement. No further evaluation was performed at that time, and the hearing loss was attributed to a viral infection.

A brain MRI following admission here demonstrated an enhancing sellar lesion that extended beyond the sella turcica into the right cavernous sinus and along the right optic nerve (Figure 4C and D). A detailed ophthalmology examination demonstrated panuveitis. Lumbar puncture showed a lymphocytic pleocytosis (CSF WBC, 250 WBC/mm³ [95% lymphocytes]) and an elevated protein (179 mg/dL [normal, 10–44 mg/dL]). Flow cytometry was negative for malignant cells, and a detailed infectious workup of the CSF was unrevealing. The serum and CSF concentrations of angiotensin-converting enzyme were normal. A CT scan of the chest and abdomen showed no lymphadenopathy or other lesions above the diaphragm but demonstrated retroperitoneal lymphadenopathy and splenomegaly. The patient underwent a transphenoidal biopsy of the sellar mass, the

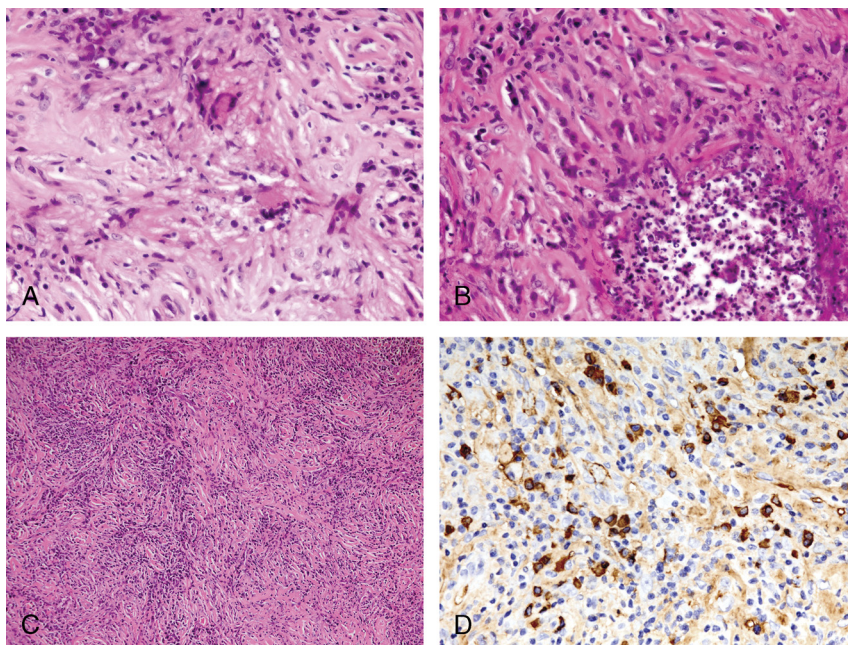


FIGURE 3. Histopathologic findings in pachymeningitis caused by granulomatosis with polyangiitis (GPA). A. (Case 6) GPA—multinucleated giant cells seen in a meningeal biopsy. B. GPA—microabscess surrounded by histiocytes. C. GPA—storiform fibrosis is present in this example. D. A case of GPA with markedly elevated numbers of IgG4+ plasma cells. [This figure can be viewed in color online at <http://www.md-journal.com>.]

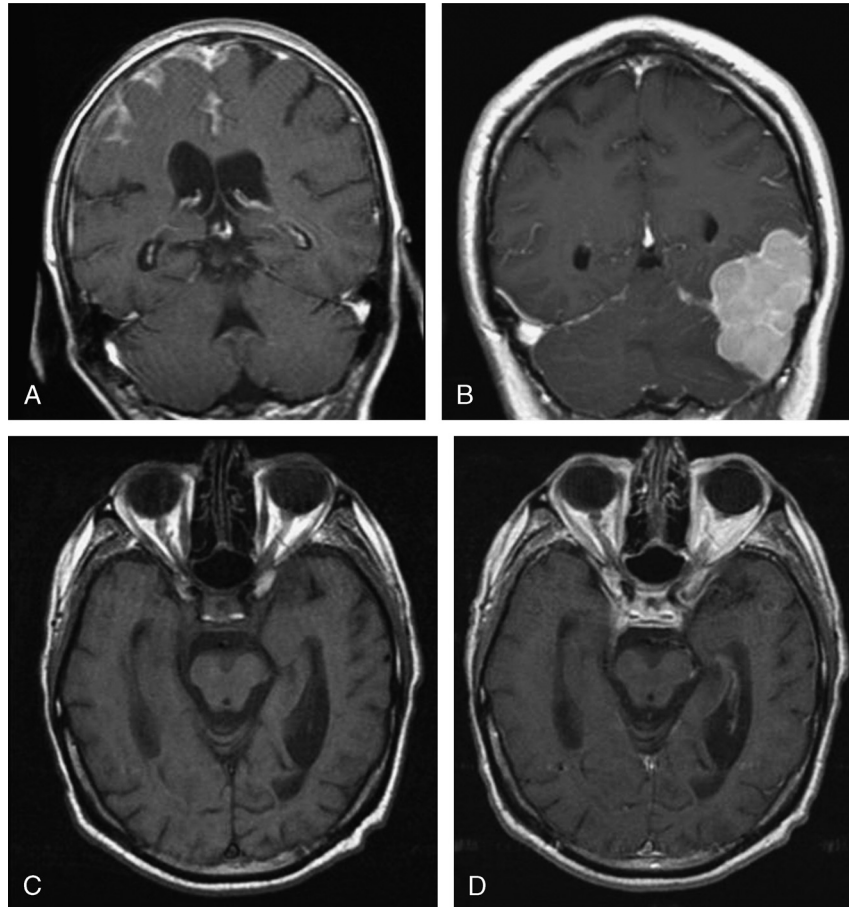


FIGURE 4. MRI findings of non-IgG4-related pachymeningitis. A. Rheumatoid arthritis-associated pachy- and leptomeningitis: coronal T1 postgadolinium MRI showing left frontal and falx pachymeningeal enhancement with prominent leptomeningal enhancement in the left frontal lobe and bilateral medial frontal lobes. B. (Case 11) Lymphoma: coronal T1 postgadolinium MRI shows a multilobulated extraaxial 3.4 × 5.7 × 6.0 cm homogeneously enhancing mass arising from the tentorium and causing mass effect on the left temp/parieto-occipital junction and left cerebellum. C and D. (Case 10) Neurosarcoidosis: axial T1 MRIs before (C) and after (D) administration of gadolinium MRI performed 1 year after initial symptoms show supra-sellar, cavernous sinus, and clival enhancement.

pathologic evaluation of which revealed scar tissue but no other abnormalities. Additional lymph node biopsies showed reactive hyperplasia.

One year after the initial presentation, the patient was readmitted for worsening gait instability and agitation. An MRI revealed stable basilar meningitis but also identified diffuse leptomeningal enhancement. A dural biopsy revealed ill-defined non-necrotizing granulomas but no lymphoplasmacytic infiltrate, storiform fibrosis, vasculitis, or eosinophils. Staining for acid-fast bacilli, Grocott methenamine silver stain, and a mucicarmine stain were all negative for infectious organisms. Immunostaining revealed 40 IgG4+ plasma cells/HPF. An enzyme immunoassay for ANCA was negative. The patient was treated for neurosarcoidosis with the combination of methylprednisolone pulses followed by prednisone and azathioprine.

Case 11: Lymphoma

A 52-year-old man presented with dizziness, a left posterior headache, and a sensation of fullness in his ears. These symptoms, attributed initially to allergies, responded to antihistamines and a short course of prednisone (dose unknown). A CT scan obtained several months after his presentation because of symptom recurrence and the development of new sinus complaints revealed an

enhancing mass in the left tentorium that extended above and below the tentorium into the upper cerebellum and left posterior temporal lobe. This finding was confirmed by MRI (Figure 4B). A lumbar puncture was not performed because of the mass effect in the posterior fossa. Biopsy of the lesion revealed monomorphic sheets of small lymphocytes, most consistent with a low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, with no evidence of extracranial disease. IgG4+ plasma cells were not identified. He was treated with surgical resection and radiation therapy.

Clinical, Radiologic, and Pathologic Features of Pachymeningitis

Symptoms

Table 1 summarizes each patient’s presentation, including diagnosis, disease site, neurologic symptoms, and CSF characteristics. The most common symptom was headache (4/14 or 29%). Other symptoms and signs, corresponding to the sites of patients’ anatomic lesions, included cranial nerve palsies, diplopia, and gait instability. Most cases of HP were identified within the cranial as opposed to the spinal meninges, but 1 patient with IgG4-RD had involvement of the lumbar dura and 1 with GPA had involvement of the thoracic dura.

TABLE 2. Histopathologic Features of Pachymeningitis Patients

Case	Diagnosis	Lymphoplasmacytic Infiltrate	Storiform Fibrosis	Phlebitis	EOS	Granulomas	Giant Cells
1	IgG4-RD	Y	Y	N	N	N	Y
2	IgG4-RD	Y	Y	Y	Y	Y (few)	N
3	IgG4-RD	Y	Y	N	N	N	N
4	IgG4-RD	Y	Y	Y	Y	N	N
5	GPA	Y	N	N	Y	Y	Y
6	GPA	N	Y	N	N	N	Y
7	GPA	Y	Y	N	N	Y	Y
8	Rheumatoid arthritis	Y	N	N	N	Y	Y
9	Giant cell arteritis	N	N	N	N	N	N
10	Sarcoidosis	Y	N	N	N	Y	N
11	Lymphoma	Y	N	N	N	N	N
12	Lymphoma	Y	N	N	N	N	N
13	Undifferentiated	Y	N	N	N	N	Y
14	Undifferentiated	N	N	N	N	N	N

Abbreviations: EOS = eosinophilia.

CSF Studies

Lumbar puncture demonstrated a lymphocytic pleocytosis in 6 of the 8 patients in whom this procedure was performed (see Table 1), with total cell counts that ranged from 6 to 378/mm³. There was an elevated protein in 50% of the cases. Lumbar puncture was not helpful in distinguishing among the different etiologies of HP in this study. IgG4 concentrations were not measured in any CSF samples.

Serologic Testing

Serum IgG4 measurements, available for 2 cases of IgG4-RD, were normal in both. Cases 5 and 6 (GPA) both had strongly positive myeloperoxidase-ANCA assay results, but Case 7, who had histopathologically proven GPA, was ANCA negative. Case 8 (rheumatoid arthritis) was strongly rheumatoid factor positive but anticyclic citrullinated peptide antibody negative.

Histopathology

Table 2 describes the histopathologic characteristics of each case. All 4 cases of IgG4-RD demonstrated classic histopathology including a dense lymphoplasmacytic infiltrate with storiform fibrosis. Storiform fibrosis was observed in the biopsies of 2 GPA patients (Cases 6 and 7), as well, but not in any other cases. Obliterative phlebitis and tissue eosinophilia, typically but not invariably features of IgG4-RD, were found in IgG4-RD Cases 2 and 4, respectively. Multinucleated giant cells and granulomas were rare in IgG4-RD but noted in Cases 1 and 2, respectively.

Immunostaining

Among the IgG4-RD cases, the mean number of IgG4+ cells/HPF was 51 cells/HPF (range, 11–98 cells/HPF) and the mean IgG4+/IgG+ ratio was 62% (range, 35%–90%) (Table 3). A variable but occasionally striking IgG4+ plasma cell infiltrate was also noted in cases of GPA, rheumatoid arthritis, neurosarcoidosis, and lymphoma. The average number of IgG4+ cells/HPF in the non-IgG4-RD cases was 24 IgG4+ plasma cells/HPF (range, 23–256 cells/HPF), and the average IgG4+/IgG+ ratio was 56% (range, 25%–96%).

Imaging

Table 4 describes the radiology findings in each case. MRI was particularly essential in patient evaluations. Figures 1 and 4 depict representative MRI findings from this series. Meningeal enhancement is appreciated most effectively by reformatted sagittal and coronal images that allow one to visualize this feature along the tentorium and posterior fossa structures. MRI abnormalities in the IgG4-RD cases were characterized by focal inflammation with a tendency toward hypertrophy and mass effect, consistent with the propensity of this disease to form mass lesions. Other etiologies of HP, particularly GPA, were more likely to be associated with diffuse meningeal involvement, but broad generalizations across the different diagnoses are limited by the relatively small number of cases.

The distribution of pachymeningitis in the setting of GPA was variable. Both diffuse and regional distributions (for example, the posterior fossa and thoracic spine) were observed. An additional

TABLE 3. IgG4+ Plasma Cell Counts

Case	Clinical Diagnosis	IgG4+ Cells/HPF	IgG4+/IgG+ Ratio (%)
1	IgG4-RD	45	90
2	IgG4-RD	161	51
3	IgG4-RD	98	70
4	IgG4-RD	11	35
5	GPA	156	96
6	GPA	0	0
7	GPA	30	50
8	Rheumatoid arthritis	23	54
9	Giant cell arteritis	0	0
10	Sarcoidosis	40	—
11	Lymphoma	0	0
12	Lymphoma	23	25
13	Undifferentiated	0	0
14	Undifferentiated	0	0

TABLE 4. Radiologic Features of Pachymeningitis Patients

Case*	Diagnosis	Type	Distribution	Thickness/Texture	T2 Flair Changes
1	IgG4-RD	Pachy	Dominant falcine lesion	Nodular with mass effect	N
2	IgG4-RD	Pachy	Dominant involvement in meninges contiguous to diseased R mastoid air cells	Smooth texture and homogenous enhancement	N
3	IgG4-RD	Both	Dominant L frontoparietal lesion & R jaw and skull base involvement	Smooth texture and homogenous enhancement	N
4	IgG4-RD	Pachy	Pachymeningeal thickening of both dura investing R L5 nerve root and the nerve itself	NA	NA
5	GPA	Pachy	Thoracic spine T2 to conus	Areas of mass effect on cord	Y
6	GPA	Pachy	Mostly tentorium and left posterior fossa	Thickened tent at 6 mm	Y
8	Rheumatoid arthritis	Lepto	L frontal, R frontoparietal and occipital	Mostly linear with “micronodular” foci	NA
9	Giant cell arteritis	Pachy	Diffuse	2–3 mm thickness	N
10	Neurosarcoidosis	Pachy	Multifocal involvement with dominant lesion in the L sella, encasing both carotids and extending laterally	Homogenously enhancing but with regions of mass effect particularly in the R Meckel cave and L medulla	Y
11	Lymphoma	NA	Focal mass in L tentorium	3.4 × 5.7 × 6 cm mass	N
12	Lymphoma	Pachy	Dominant enhancing lesion in the L cavernous sinus and sella and extending to the dura of the L anterior temporal lobe. Thoracic dural mets.	Homogenously enhancing mass	Y
13	Undifferentiated	Pachy	Diffuse including spine associated with venous sinus thrombosis	Hypertrophic	N
14	Undifferentiated	Pachy	Diffuse	Thin	Mild

Abbreviations: L = left, Lepto = leptomeningitis, NA = not applicable, Pachy = pachymeningitis, R = right.

*Images from Case 7 were unavailable for review.

feature seen in the 3 GPA patients was scattered periventricular and subcortical white matter T2 hyperintensities. These nonspecific findings are observed commonly in patients with long-standing microvascular disease caused by diabetes and hypertension, but neither of these problems was an issue for the IgG4-RD patients in the current study.

Posttreatment Imaging

Serial imaging in 2 cases suggests that radiologic improvement occurs in some patients. Case 2 had a complete clinical and radiographic response to rituximab after a failed trial of glucocorticoids. Case 3 had clinical and radiographic improvement without any immunosuppressive/immunomodulatory therapy.

DISCUSSION

This series demonstrates that IgG4-RD accounts for a substantial proportion (66.6%) of cases of “idiopathic” HP and may be in fact the most common etiology of this condition. The link between HP and IgG4-RD has been recognized previously, but to our knowledge this is the first study attempting to compare the frequency of IgG4-RD as the cause of pachymeningitis to that of other disorders known to cause this condition.^{5,6,16,21,28,36} An important strength of our study was the use of recently published consensus guidelines for the diagnosis of IgG4-RD that reflect the prevailing opinions of the world’s experts in this condition.¹⁰ IgG4-RD was responsible for 4/14 (29%) of the cases in this series, compared with 3 cases associated with GPA (21%), 2 with lymphoma (14%), 2 undifferentiated cases (14%), and 1 case each occurring in the setting of rheumatoid arthritis, giant cell arteritis, and sarcoidosis. Except for the idiopathic cases identified as

IgG4-RD, no other original diagnoses were amended. All of these conditions must be considered in cases of noninfectious HP.

The high proportion of IgG4-related HP cases has important implications for both internists and neurologists. IgG4-RD has the potential to cause lesions at multiple anatomic sites, either synchronously or metachronously.⁴³ Previous descriptions of HP suggest similar behavior, as “idiopathic” cases have been reported in association with orbital pseudotumor, lung nodules, interstitial nephritis, sclerosing cholangitis, and retroperitoneal fibrosis.^{2,4,6,13,24,25,30,30,48,50} One of the 4 IgG4-RD patients (Case 2) reported in the current study also had histopathologically verified disease in her mastoid sinus, and it is possible that the “Tolosa-Hunt syndrome” experienced by Case 1 14 years before presentation was also a complication of IgG4-RD. Other known central nervous system (CNS) manifestations of IgG4-RD include IgG4-related hypophysitis^{21,27,39} and cerebral parenchymal lesions.²³

The histopathologic features in IgG4-RD are crucial to the diagnosis. The major histopathologic features include a dense lymphoplasmacytic infiltrate, storiform fibrosis, and, in many tissues, obliterative phlebitis. Mild to moderate tissue eosinophilia and nonobliterative phlebitis have also been associated with IgG4-RD.^{10,40} A cutoff of >10 IgG4+ plasma cells/HPF is compatible with the diagnosis of IgG4-RD, provided that this finding is associated with an IgG4+/total IgG+ plasma cell ratio of >40% and histopathologic findings consistent with those described above.¹⁰

A common misconception is that the presence of an unexpectedly high number of IgG4+ plasma cells/HPF is diagnostic of IgG4-RD. The pathologic findings in the current series underscore the concept that the essence of IgG4-RD pertains to far more than simply the number of IgG4+ plasma cells within a sample.^{10,44} Cases of GPA (Case 5), rheumatoid arthritis (Case 8),

neurosarcoidosis (Case 10), and lymphoma (Case 12) all had more than 10 IgG4+ plasma cells/HPF. In fact, 1 GPA case (Case 5) had the highest number of IgG4+ plasma cells/HPF in the series. On average, the number of IgG4+ plasma cells/HPF was lower in the non-IgG4-RD cases (average, 24 vs. 51 cells/HPF), but the range was wide. Similarly, an elevated ratio of IgG4+/IgG+ plasma cells is not specific to IgG4-RD and can be found in other conditions. For example, the meningeal biopsy from the rheumatoid arthritis patient (Case 8) had an IgG4+/total IgG+ plasma cell ratio of 0.54.

The characteristic histopathology of IgG4-RD distinguishes it from other diseases known to cause pachymeningitis. Granulomatous diseases such as GPA, rheumatoid arthritis, and sarcoidosis are important considerations in the differential diagnosis of HP. The presence of multinucleated giant cells or other manifestations of significant granulomatous inflammation are uncommon in IgG4-RD but may be present. The biopsy for Case 1 showed multinucleated giant cells. The biopsy in Case 2 showed a few granulomas in the dura but in the setting of otherwise classic pathology of IgG4-RD as well as similarly typical IgG4-RD findings in the mastoid biopsy, these were not thought to suggest an alternative diagnosis. Necrotizing vasculitis is also a clue that an entity other than IgG4-RD is operative.

The majority of patients in the current case series had a lumbar puncture as part of their evaluation. Regardless of HP etiology, the lumbar puncture most commonly revealed a lymphocytic pleocytosis and elevations in the CSF protein, which is similar to the observations of other investigators.²⁵ However, the CSF findings did not permit distinctions among the causes of pachymeningitis in this series, because GPA, rheumatoid arthritis, sarcoidosis, and giant cell arteritis were also associated with a lymphocytic pleocytosis and elevated CSF protein concentrations. IgG subclass analyses were not available on any patient in this study. Thus, although lumbar puncture can identify a CSF profile that is typical of noninfectious and nonmalignant causes of pachymeningitis, the principal value of this procedure is in the exclusion of infection and cancer. The potential utility of measuring IgG4 levels in the CSF to diagnose IgG4-RD has been suggested but not confirmed, to our knowledge.⁴⁶ It is possible that multiple non-IgG4-RD conditions can cause elevations in the CSF IgG4 concentration, as is true for the serum.

Contrast-enhanced MRI is valuable in identifying the lesion, but the radiologic appearance of the lesions varies considerably from case to case and is not diagnostic of any particular disease entity. The current study was too small to establish any single MRI pattern as highly characteristic of IgG4-RD. However, the focal or pauci-focal distribution of changes within the meninges, observed sometimes with mass effect, is consistent with previously reported cases of IgG4-related pachymeningitis in which meningeal hypertrophy has led to mass lesions associated with compression of the brain or spine parenchyma and blood vessels.^{8,17,23,24,28}

Among the cases of GPA-associated pachymeningitis reported here, the distribution of meningeal enhancement ranged from diffuse to localized, consistent with previous reports.³¹ Nonspecific scattered white matter T2 hyperintensities have been reported in more than half of GPA patients with possible CNS involvement.³¹ In the current series, such nonspecific white matter changes were detected in older patients with GPA, rheumatoid arthritis, neurosarcoidosis, and lymphoma, but not in patients with IgG4-RD. The future utility of other imaging modalities such as positron emission tomography (PET)-CT in both IgG4-related pachymeningitis and other forms of IgG4-RD is unclear, but has been previously suggested.^{32,34}

IgG4-related pachymeningitis can be contiguous with sinus disease, as observed in Case 2. In this clinicoradiologic feature,

IgG4-RD is similar to GPA, a disorder in which direct extension of sinus involvement into the CNS is known to occur. A similar case reported by Kosakai et al²⁴ described a 54-year-old patient whose left-sided orbital pseudotumor extended through the orbital roof and was contiguous with the pachymeninges. Thus, contiguous sinus and meningeal involvement in pachymeningitis is a feature of both GPA and IgG4-RD.

Treatment of hypertrophic meningitis should be targeted at the underlying systemic process identified. The natural history of IgG4-RD is variable and some patients experience spontaneous remission, at least temporarily (for example, Case 3). For IgG4-RD, the standard first-line treatment is glucocorticoids.²² Although glucocorticoids are often effective in quieting disease activity or inducing remission, their effect is rarely durable, as illustrated by the experiences of Cases 1 and 2.²² Treatments that both spare patients from the potentially noxious effects of high-dose glucocorticoids and induce robust remissions are now under investigation. Rituximab has recently been demonstrated to be effective in allowing discontinuation of all immunosuppressants with persistent remission in a number of IgG4-RD patients.^{19,20} Both of the IgG4-RD patients (Cases 1 and 2) in the current series who were treated with rituximab demonstrated significant clinical and radiologic treatment responses.

This retrospective case series demonstrates that IgG4-RD accounts for a significant portion of HP cases previously thought to be idiopathic in nature. To our knowledge, this series is the first to diagnose IgG4-RD based on 2012 consensus guidelines for interpretation of the pathology of this condition.¹⁰ Meningeal biopsy was crucial to diagnosing the systemic causes in each of the HP cases. Neither CSF evaluations nor cross-sectional imaging studies are sufficiently specific to distinguish among the various diagnostic possibilities. If the diagnosis cannot be clarified through biopsy of a non-CNS organ and if the serologic examination is unrevealing, then adequate sampling of the meninges may be essential to securing the correct diagnosis.

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ERRATUM

Comparison of Clinical Manifestations and Outcome of Community-Acquired Bloodstream Infections Among the Oldest Old, Elderly, and Adult Patients: Erratum

In the article “Comparison of Clinical Manifestations and Outcome of Community-Acquired Bloodstream Infections Among the Oldest Old, Elderly, and Adult Patients” by Lee et al, appearing in *Medicine (Baltimore)*, Volume 86, No. 3, on page 138, the DOI provided for this article was incorrect. The correct DOI is: 10.1097/MD.0b013e31806a754c.

REFERENCE

Lee CC, Chen SY, Chang IJ, Chen SC, Wu SC. Comparison of clinical manifestations and outcome of community-acquired bloodstream infections among the oldest old, elderly, and adult patients. *Medicine (Baltimore).* 2007;86:138–144.