Cerebral Venous Sinus Thrombosis and Pachymeningitis in IgG4 Related Disease: Report of Two Cases and Review of Literature

Dear Sir,

Immunoglobulin G4-related disease (IgG4-RD) is a systemic disorder characterized by an inflammatory reaction, rich in IgG4-positive plasma cells associated with sclerosis.[1] The disease spectrum includes autoimmune pancreatitis, Mikulicz disease, pseudotumor of the lung, tubulointerstitial nephritis, and Riedel thyroiditis. Central nervous system involvement in IgG4-RD is rare, and usually manifests with hypertrophic pachymeningitis (HP), hypophysitis, and orbital pseudotumor. Hypertrophic pachymeningitis is also observed in many other conditions including infectious diseases (e.g., neurosyphilis, tubercular, bacterial, and fungal meningitis), inflammatory disorders (e.g., granulomatosis with polyangitis, giant-cell arteritis, rheumatoid arthritis, and neurosarcoidosis), and malignancies (e.g., dural carcinomatosis, metastasis from adjacent skull bone or brain, meningioma, and lymphomas). Hypertrophic pachymeningitis may be the only manifestation in IgG4-RD without involvement of other organs with normal to mildly increased serum IgG4 concentrations. Symptoms include headache, neck pain, cranial nerve palsies,

hydrocephalus, seizure, motor weakness, sensory loss, or features of myeloradiculopathy. In the available medical literature, there is paucity of reports of cerebral venous sinus thrombosis (CVST) secondary to HP in IgG4-RD.[2,3] In our cohort of 172 patients with CVST, two were due to IgG4-RD pachymeningitis. In this communication, we report these two CVST patients with IgG4-RD hypertrophic pachymeningitis in the light of reported literature.

Patient # 1: A 31-year-old male presented with 4 episodes of recurrent unilateral visual loss in past 21 months. In the first episode, he developed acute onset, painless blurring in left eye which progressively deteriorated to perception of light over 20 days. He did not have any other neurological and systemic symptoms. He was diagnosed as optic neuritis and treated with methyl prednisolone for 5 days followed by oral prednisolone for 10 days. He had three more such episodes, second one in the right eye. His vision improved after the initial three attacks, but visual loss persisted to finger count at 1 meter after the 4th attack. Six months back, he developed one episode of left focal convulsive seizure for 2 min with unconsciousness and received tablet sodium valproate 500 mg twice daily. Three months back, he developed acute paraparesis. There was no paresthesia, bowel bladder involvement, flexor spasms or dysarthria. He was non-diabetic, non-hypertensive, and did not suffer from tuberculosis. His blood pressure was 110/70 mm of Hg, pulse rate 80/minute, and respiratory rate 14/minute. His cardiovascular, respiratory, and abdominal examinations were unremarkable. He was conscious, oriented, and his Mini Mental Status Examination score was 29/30. Vision in right eye was 6/12 and in left eye finger counting at one meter. Color vision was impaired bilaterally, left more than right. Fundus examination revealed temporal pallor bilaterally. He had spastic paraparesis of grade 3, brisk knee, and ankle reflexes with extensor plantar response bilaterally. Sensory and cerebellar examinations were normal. Cranial MRI revealed pachymeningitis along with bilateral frontal gliotic changes. Magnetic resonance venography showed superior sagittal sinus (SSS) and straight sinus thrombosis [Figure A1 and A2]. MRI spine was unremarkable. Laboratory testing revealed normal hemoglobin, blood counts, kidney, liver, and thyroid function tests. Erythrocyte sedimentation rate was 10 mm at first hour. C-reactive protein was 1.10 mg/dl. His cerebrospinal fluid analysis was normal. HIV serology was negative. Serum ACE level was 28U/L (8-52 U/L), vitamin B12 level 1236pg/ml, and homocysteine 13.1μmol/L. Antinuclear antibody, anti-double stranded DNA antibody, antiphospholipid antibody, and p and c-ANCA were negative. Protein C, protein S and antithrombin III levels were within normal limits. Factor V Leiden mutation was negative. Serum IgG level was 2000 mg/dl (normal 800–1800 mg/dl) and IgG4 was 3.2 gram/L (normal 0.03–2.01gram/L). Hence a diagnosis of CVST secondary to IgG4-RD HP was considered. He was prescribed tablet prednisone 40 mg daily, oral anticoagulant, and tizanidine 2 mg three times daily. Sodium valproate was continued. At 5 months of follow up, he had mild spastic lower limb weakness and was independent for activities of daily living. Vision in left eye did not improve and his repeat cranial MRI revealed partial resolution of pachymeningitis and persistence of sinus thrombosis [Figure A3 and A4].

Patient # 2**:** A 46-year-old male presented with headache since 6 months. He is non-diabetic, non-hypertensive, and did not have any systemic features. His blood pressure was

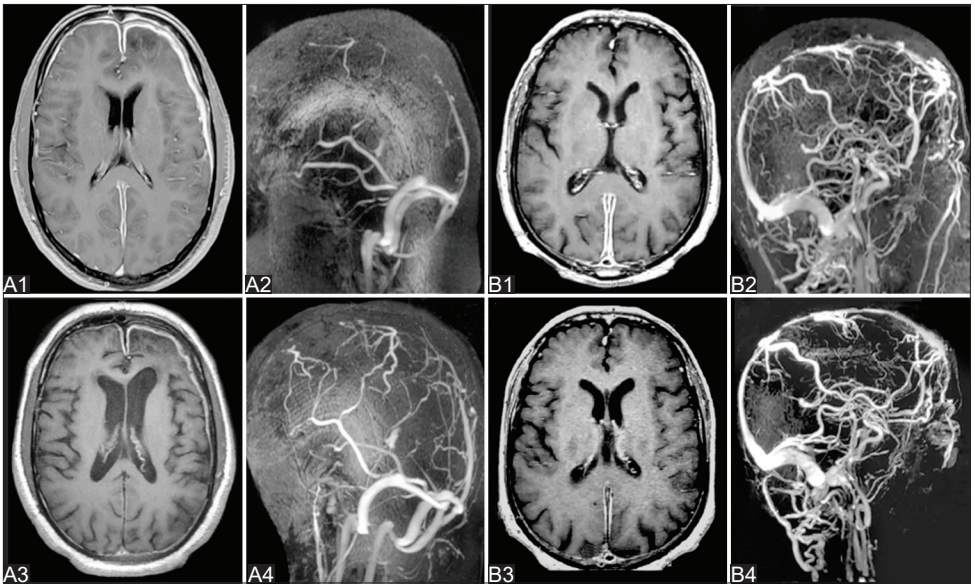

Figure 1: T1 contrast MRI and MR venography in two patients with IgG4-related disease. MRI of patient # 1 show (A1) hypertrophic pachymeningitis in falx cerebri and left side hemisphere at baseline which only partially resolved at 3-month follow up (A3). MR venography of the same patient at base line (A2) shows superior sagittal sinus (SSS) and straight sinus thrombosis which remained occluded at 3-month follow up (A4). MRI of the patient # 2 also shows pachymeningitis (B1) which resolved partially at 3-month follow up (B3). MRV of the same patient shows thrombosis of straight sinus and SSS (B2) which remained occluded at follow up except partially recanalized SSS (B4)

Table 1: Number of published literature of cerebral venous sinus thrombosis/stenosis in patients of hypertrophic cranial pachymeningitis

Author/Year	Age/Gender	Thrombosed sinuses	Treatment	Recanalization
Kioumehr *et al*.,1994[5]	35/M	Transverse sinus	NA	NA
Goyal *et al*., 1997[6]	19/F	Dural sinus thrombosis	Steroid	NA
Yunten *et al*., 1999[7]	30/F	Pansinus thrombosis	Steroid, azathioprine	No recanalization
Hamada *et al*., 2000[8]	64/M	Dural AVF of straight sinus	Embolization, excision of straight sinus, steroid	
Lee *et al*., 2003[9]	23/F	Straight sinus	Prednisolone and azathioprine	NA
Oiwa *et al*., 2004[10]	44/M	Pan sinus thrombosis	Anticonvulsant	No recanalization
Lampropoulos *et al*., 2006[11]	63/M	Cerebral venous sinus thrombosis	Oral steroid + azathioprine	NA
Singh *et al*. 2009[12]	49/f	Posterior SSS, bilateral transverse and sigmoid sinuses.	Oral steroid	NA
Bhatia *et al*. 2009[13]	38/M	Posterior SSS, torcula, bilateral transverse sinus , and left proximal sigmoid sinus.	Pulse steroid followed by oral steroid	No recanalization
	23/M	Posterior SSS, right transverse sinus, right sigmoid, and straight sinus.	Intravenous dexamethasone for 1 week followed by oral prednisolone with tapering doses	Recanalized except partial recanalization of straight sinus
Xia *et al*. 2010[14]	42/F	SSS	Steroids, azathioprine, mycophenolate, adalimumab and methotrexate	No recanalization
Saito T *et al*. 2014[15]	72/F	Confluence of sinus, straight sinus, right transverse sinus	Steroid	NA
Zhao *et al*., 2014[16]	44/F	Stenosis	Steroid	NA
	40/F	Occlusion	Steroid	
	41/M	Occlusion	Steroid, azathioprine	
	17/F	Stenosis	Steroid	
	71/F	Stenosis	Steroid	
Nayak R *et al*. 2018[17]	23/M	Left transverse and sigmoid sinus, left jugular vein	Ceftazidime, cotrimoxazole	NA
Kuribayashi *et al*. 2019[18]	58/M	SSS	Steroid, cyclophosphamide	Recanalized
Di Stefano V, *et al*. 2019[19]	47/F	SSS, transverse and sigmoid sinus	Steroid, cyclophosphamide, rituximab	Recanalized

AVF= arteriovenous fistula, CSF= cerebrospinal fluid, F=female, M=male, NA=not available, SSS= superior sagittal sinus

130/80 mm Hg and pulse rate 78/minute. Systemic and neurological examinations were normal. Cranial MRI revealed diffuse pachymeningeal thickening. Magnetic resonance venography revealed straight sinus and anterior two-third SSS thrombosis [Figure B1 and B2]. His blood count, kidney, liver, and thyroid function tests, urine examination and radiograph of chest were normal. Erythrocyte sedimentation rate was 30 mm at first hour and C-reactive protein was 2.64 mg/dl. His vitamin B12 and homocysteine levels were normal. Protein C activity was 126% (70–130%), protein S 76% (65–140%), and antithrombin III 120% (80–120%). Autoimmune profile including antinuclear antibody, anti-double stranded DNA, antiphospholipid antibody, p and c-ANCA were negative. Factor V Leiden mutation was negative. His serum IgG level was 2020 mg/dl and IgG4 level was >3.6 gram/L (0.03–2.01 gram/L). A diagnosis of CVST secondary to IgG4-RD HP was made, and he was advised tablet prednisone 0.5 mg/kg body weight along with oral anticoagulant. His international normalized ratio was maintained between 2.5 to 3. At one-month follow up, his headache has resolved completely and repeat MRI with MRV at 3 months revealed partial resolution of pachymenigitis and incomplete recanalization of SSS [Figure B3 and B4].

Both patients had CVST due to IgG4-RD hypertrophic pachymeningitis which was confirmed by raised serum IgG4 level and absence of other CVST risk factors. IgG4-RD is a systemic inflammatory disease characterized by elevated serum IgG4 levels, abundant infiltration of IgG4-positive plasma cells and high-grade sclerosis of the affected region. B-cell–dependent activation of pathogenic CD4+ T cells mediates inflammation and fibroblast activation which lead to collagen deposition, resulting in tissue hypertrophy and increased dural thickness. Meningeal IgG4-RD manifests mainly as pachymeningitis of the brain or spinal cord**.** Pachymeningitis patients have variable manifestations; supratentorial HP

involvement leads to traction resulting in referred pain to the trigeminal nerve distribution whereas infratentorial HP leads to referred pain to the vertex, ear, occiput, or upper neck. Hypertrophic pachymeningitis may cause encasement and compression of optic nerve leading to visual deficit or visual field defect due to compression of optic chiasm or optic tract. There may be weakness, sensory loss, and seizures as a result of cortical involvement**.** The involvement of spinal dura mater may lead to myelopathy, radiculopathy, or myeloradiculopathy syndrome.[1] Visual loss in first case is likely due to compression of optic nerve. He had SSS thrombosis and bilateral frontal lesions on MRI which may account for his paraparesis.

Cerebral venous sinus thrombosis has been reported in the patients with idiopathic HP. A review by Huang *et al*. reported 17 CVST patients secondary to idiopathic HP.[4] In total, there are 20 patients with CVST associated with HP [Table 1]. The etiology of pachymeningitis were idiopathic in 16, ANCA associated vasculitis in 3 and burkholderia infection in 1. None had IgG4-RD.[5-19] Recanalization occurred in 3/7 patients. There is paucity of report on CVST in association with IgG4 related HP. Ekizoglu *et al*., reported a 47-year-old woman with headache and visual impairment, who had CVST secondary to IgG4 related pachymeningitis.[2] Sireesha, *et al*. also reported superior sagittal sinus thrombosis in one out of six patients with HP secondary to IgG4-RD. All the patients were biopsy proven with elevated IgG4 in 50% patients. All received steroid therapy while Rituximab was administered in three patients and azathioprine to one patient.[3] In this context, the two cases with CVST and HP with elevated IgG4 level are representative of rare occurrence. The mechanism of CVST in IgG4-RD is not well understood; venous stasis due to compression of sinuses by HP as well as hyperviscosity may contribute to thrombosis of dural sinuses.[4,20]

It is important to recognize IgG4-RD as a risk factor of CVST because these patients need immunosuppressants along with anticoagulant. Most of the patients with IgG4-RD with multiorgan involvement respond to glucocorticoid treatment leading to resolution of lesion and decrease in serum IgG4 level within few weeks. Additional immunosuppressant such as azathioprine, mycophenolate mofetil or rituximab may be used in steroid resistant or dependent patients. Both of our patients improved although visual loss persisted. The sinuses and pachymeningitis improved partially.

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Informed consent

Written informed consent was obtained from all subjects (patients) in this study**.**

Ethical approval

This study was ethically approved by the Institutional Ethics Committee, SGPGIMS (PGI/BE/774), and Lucknow, India

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Conflicts of interest

There are no conflicts of interest.

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