Clinico-Pathological Features in Köhlmeier–Degos Disease with Cutaneous and Neurological Involvement

Sir,

Köhlmeier–Degos disease or Degos disease or malignant atrophic papulosis is a rare chronic obliterative vasculopathy of uncertain etiology. It affects skin and other organs such as the gastrointestinal tract and the central nervous system, in addition to the heart, lungs, kidneys, and eyes.[1] It can be classified as (i) malignant Degos disease with systemic manifestations which is further subclassified as (a) autoimmune: when there are associated clinical and/or laboratory features of either connective tissue disease or vasculitis, (b) coagulopathy-associated, and (c) virally induced, and (ii) benign cutaneous type which lacks systemic manifestations even after years of onset.[1] The disease usually manifests in adults, has male preponderance, and has been more commonly reported from the Caucasian population.[1] We describe the clinical course in a patient with Degos disease having neurological involvement and highlight the imaging and histological findings.

A 44-year-old gentleman developed one episode of focal-to-bilateral tonic–clonic seizure. Examination four hours after the seizure was normal. He had diffuse skin lesions for about 2 years [Figure 1a and b]. He did not have preexisting scarring acne on the face. Brain MRI showed enhancing multifocal T2/FLAIR hyperintense lesions [Figure 1c–g]. Stereotactic biopsy of the right temporal lesion showed areas of coagulative necrosis/infarct which was indicative of vasculopathy/vasculitic process [Figure 2a–d]. Brain MRI after 2 months showed an increase in the size of the lesions [Figure 1 h,i, and j]. The histopathological findings of skin biopsy are depicted in Figure 3a–d. He was treated empirically with intravenous methyl prednisolone (1 g/day for 5 days). One month later, he developed sudden onset, non-progressive, impaired vision in the right eye. Examination revealed bilateral optic disc edema, soft retinal exudates, and right inferior temporal quadrantanopia. Brain MRI done 4 days after the onset of new deficits showed no new lesions. There was evidence of "blooming" in susceptibility-weighted images within these lesions [Figure 1k and l]. Hematological and biochemical investigations were significant for an elevated erythrocyte sedimentation rate (52 mm/first hour). Work up for immune-mediated and granulomatous disorders and serological testing for human immunodeficiency virus, hepatitis B, and hepatitis C viruses were negative. Cerebrospinal fluid analysis showed normal opening pressure and slightly elevated protein (50.9 mg/dL, ref.: 15–45 mg/dL). CT scan of chest and abdomen was normal. Based on the clinical and histological findings of the characteristic skin lesions, the patient was diagnosed to have Degos disease. He was treated with monthly pulsed intravenous methylprednisolone along with levetiracetam, clopidogrel, and cilostazole. His visual deficits remained status quo. There was no recurrence of seizures. Skin lesions increased in number. He developed gastrointestinal symptoms in the form of vomiting and diarrhea alternating with constipation and he succumbed to his illness around one year after onset of neurological symptoms.

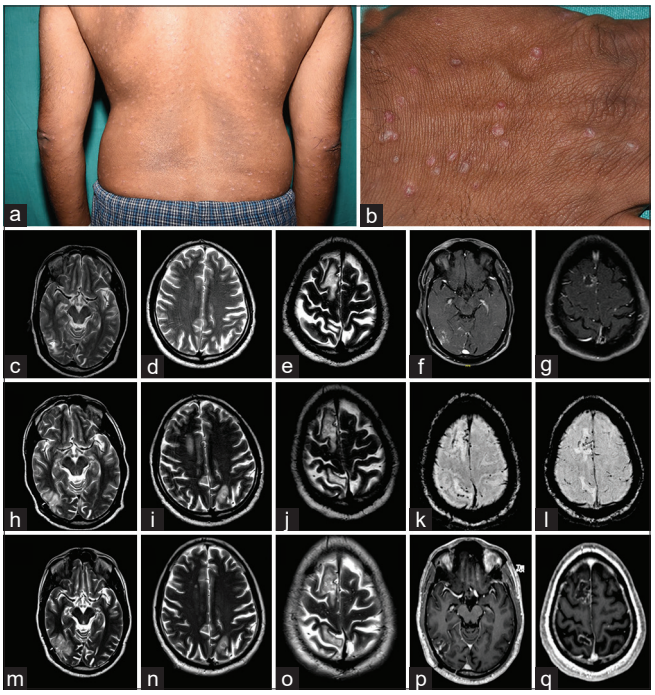

Figure 1: (a, b) Clinical photographs showing papular skin lesions with a porcelain-white center and erythematous margin over the posterior aspect of trunk and limbs. (c–e) Axial sections of brain MRI show hyperintense lesions in the right frontal and posterior temporal and left parietal in T2 sequences. (f and g) Postcontrast T1W sequences show enhancement of the periphery of lesions. (h,i, and j) Brain MRIs after 2 months of onset show increase in the size of the lesions. (k and l) Blooming seen on SWI within the lesions. (m–q) Brain MRI after the onset of visual symptoms shows persistence of the lesions

Neurological involvement is reported in 20–60% of patients with Degos disease.[2] In a case series from the Mayo Clinic, 10 out of 15 patients had neurological manifestations, including fatal hemorrhagic or ischemic strokes, polyradiculoneuropathy, and nonspecific symptoms. More than half the patients had only cutaneous manifestations.[3] As noted in our patient, the skin lesions antedate neurological manifestations by weeks to years. Uncommonly, neurological features can precede or occur simultaneously with skin lesions.[4] Any part of the neuraxis can be affected and the clinical manifestations correspond to the site of involvement. Our patient manifested with neurological and ophthalmological features in the form

of seizures, quadrantanopia, and multifocal brain lesions, which were secondary to vasculopathy of the leptomeningeal and cortical vessels. He also developed optic disc edema in the absence of raised intracranial pressure raising the possibility of optic nerve head ischemia secondary to retinal artery involvement. Table 1 summarizes the neurologic manifestations reported in literature.[2-9]

The clinical course is progressive, sometimes fulminant, with the appearance of new neurological deficits as was noted in our patient. Fatal outcome has been reported in majority of the patients.[5,7] Death occurs from bowel perforation, large cerebral infarcts, or massive cerebral hemorrhage. Rarely patients have mild or transient deficits.[10] The key determinant of mortality is the degree of vascular involvement and ischemic complications. The factors that determine whether the disorder remains benign and confined to the skin or becomes malignant with other organ system involvement are not known.

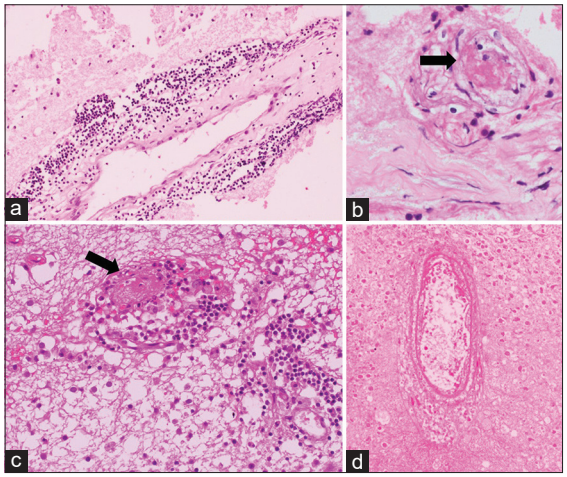

Figure 2: (a) Biopsy of the right posterior temporal brain lesion shows thickened leptomeningeal vessel with perivascular inflammation (H&E, 100×). (b and c) Cortical vessels with fibrin thrombus (arrow) and vessel wall inflammation (H&E, 200×). (d) Thrombosed vessel with parenchymal infarct (H&E, 200×)

Establishing an early and accurate diagnosis is important to ensure close follow-up for extracutaneous organ involvement. Diagnosis rests on identifying the characteristic skin lesions as noted in our patient, which is further supported by histological studies. Other neurological disorders where cutaneous lesions aid in the etiological diagnosis are listed in Table 2. Treatment of Degos disease includes immunosuppressive agents, antiplatelets, anticoagulants, rheological agents, and prostaglandins like treprostinil.[1] There is no effective treatment for Degos disease since the understanding of the underlying pathophysiology is incomplete. Increased platelet aggregation and fibrinolytic dysfunction have been noted.[1] Familial occurrence with autosomal dominant inheritance has been reported. Autoimmunity appears to play a major role as evidenced by presence of autoantibodies like antiphospholipid antibodies. Besides, as noted in our patient, histopathological findings of the skin and brain suggest vasculopathy. Other studies including autopsy-based studies provide evidence for

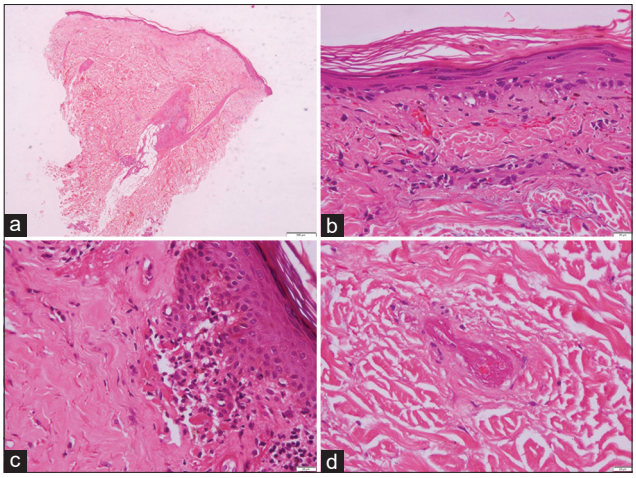

Figure 3: (a) Biopsy of skin shows thinned out epidermis (H&E, 100×). (b) Basal layer shows vacuolation (H&E, 200×). (c) Inflammatory infiltrate with karryorhectic debris is noted (H&E, 200×). (d) A dermal vessel shows sclerosis and damage to the wall (H&E, 200×)

Table 1: Neurologic manifestations of Degos disease reported in literature

Site	Presentation
Brain	Venous thrombosis, hemorrhage, infarct involving supra- or infratentorial regions leading to headache, seizures, cognitive decline, dysarthria, aphasia, hemiparesis, amaurosis fugax, brainstem dysfunction
	Tear drop calcifications in cerebral parenchyma
	Progressive unilateral occlusion of cerebral vessels leading to hemispheric atrophy and thinning of overlying calvarium
Spinal cord	Myelopathy with patchy peripheral lesions ("saw-tooth" or "moth-eaten" appearance) and thinning of cord
Peripheral nervous system	Optic neuropathy
	Radiculopathy
	Sensori-motor polyneuropathy
	Myopathy
Extra-axial	Enhancing leptomeningeal nodules
	Diffuse meningeal enhancement
	Ependymal enhancement
	Subdural effusion (due to blockage of CSF flow) can mimic battered baby syndrome in infants

Table 2: Differential diagnosis of central nervous system disorders with pathognomonic skin lesions

Disease/Syndrome	Neurological features	Cutaneous features	Histological findings
Inflammatory disorders			
APLA	Ischemic strokes, Sneddon's syndrome, transverse myelitis, chorea	Livedo reticularis, acrocyanosis, Degos-like lesions, erythematous macules, purpura, ecchymoses, and subungual splinter hemorrhages	Occlusive vascular changes, thrombotic microangiopathy, arterial intimal fibrous hyperplasia
SLE	Encephalopathy, chorea, strokes, psychosis, optic neuropathy, peripheral neuropathy, myopathy, myasthenia gravis	Photosensitivity, malar rash, discoid lupus, alopecia, mucosal ulcers, Raynaud phenomenon, angioneurotic edema, palpable purpura, subcutaneous nodules, gangrene, erythema multiforme	Vasculopathy, micro-/macro-infarction, focal/diffuse vasculopathy
Sarcoid	Cranial neuropathies, chronic meningitis, peripheral neuropathy, myopathy, hypothalamic involvement	Dry skin, hypohidrosis, cicatricial alopecia, erythema nodosum, vesicles, maculopapular rash, lupus pernio, plaques, keloids	Noncaseating granuloma
Behcet's disease	Aseptic meningitis, encephalitis, myelitis, CVT, isolated trigeminal neuralgia	Erythema nodosum, genital ulcers, oral aphthous ulcers, dermatographia, vesicles, pustules, folliculitis, pyoderma, acneiform eruptions, and necrotising vasculitis	Intense inflammatory infiltration by polymorphs, eosinophils, lymphocytes, and macrophages, necrosis, and apoptotic neuronal loss. Intense inflammatory infiltration of small vessels can occur, fibrinoid necrosis is not seen
Sjögren's syndrome	Aseptic meningitis, CVT, peripheral neuropathy, dorsal ganglionopathy	Raynaud's phenomenon, purpura, xerostomia	Necrotic lesions, perivascular cuffing
Rheumatoid arthritis	Pachymeningitis, leptomeningitis, CNS vasculitis, myelopathy, mononeuritis multiplex	Subcutaneous nodules, liver palms, vivid washable yellow discoloration	Rheumatoid nodules, pachymeningitis, leptomeningitis, vasculitis
Genetic disorders			
Tuberous sclerosis	Subependymal giant-cell astrocytomas, behavioral problems, autism, West syndrome	Ash leaf spots, confetti-like hypopigmented patches, café-au-lait spots, shagreen patches, periungual fibromas, facial angiofibromas	Cortical tubers, neuroglial hamartomas Vascular calcification
Neurofibromatosis 1 and 2	Optic nerve gliomas, radiculopathy, acoustic neuromas, schwannoma	Café-au-lait spots, fibromatous dermal tumors, and Lisch nodules, axillary or inguinal region freckling, neurofibromas, violaceous papillary skin neurofibromas	Micronodular capillary and arteriolar proliferations. Glial proliferations are hamartomatous in nature
Hereditary hemorrhagic telangiectasia (HHT)/ Osler–Weber–Rendu syndrome	Ischemic strokes, subarachnoid hemorrhages	Mucocutaneous telangiectasias	Vascular dysplasia
Homocystinuria	Ischemic strokes, mental retardation, seizures, personality disorders, depression	Cutaneous hypopigmentation, malar flush, and livedo reticularis	
Porphyrias	Encephalopathy, psychosis, neuropathic abdominal pain, peripheral neuropathy	Blisters, postinflammatory hyperpigmentation	
Sturge–Weber	Leptomeningeal venous malformation, epilepsy, developmental delay	Congenital port wine stain over the face	Tortuous, thin-walled leptomeningeal blood vessels, dystrophic mineralization in cortex and white matter, cortical atrophy, subpial gliosis, focal cortical dysplasia type Ia
Ataxia Telangiectasia/ Louis-Bar syndrome	Ataxia, choreoathetosis, seizures, oculomotor abnormalities	Cutaneous telangiectasia, café-au-lait spots, progeric and sclerodermatous changes	Loss of myelinated fibers in the posterior funicles, cortical atrophy, loss of the internal granular layer, Purkinje cell loss, empty baskets, hypertrophy of the Bergman glia, degeneration of dentate nucleus

Contd...

Table 2: Contd...

Disease/Syndrome	Neurological features	Cutaneous features	Histological findings
Fabry disease	Painful small fiber neuropathy with autonomic involvement, seizures	Purpuric, skin rash, angiokeratoma diffusum	Hydropic deep white matter, neuronal ballooning due to glycolipid storage Angiopathy of subarachnoid arteries due to medial thickening from glycolipid deposition in smooth muscles and adventitial fibrosis with lymphocytic infiltration
Pseudoxanthoma elasticum	Stroke, retinopathy	Pseudoxanthoma, multiple papules, peau d' orange, angioid streaks, subcutaneous calcification usually in blood vessels	Skin shows calcium deposits and swollen, fragmented elastic fibers
Infections			
Syphilis	Aseptic meningitis, late meningovascular syphilis, tabes dorsalis	*Primary*: Chancre. *Secondary*: maculopapular nonpruritic scaling rash, patchy alopecia, condyloma lata, mucous patches, erythema multiforme, split papules	Extensive leukocyte infiltration into the meninges, with perivascular leukocyte infiltration. Fischer's plaques
Tuberculosis	Chronic meningitis, vasculitic infarcts, Pott spine, CNS tuberculomas	Primary tuberculous chancre, verrucosa cutis, lupus vulgaris, scrofuloderma, erythema nodosum, erythema multiforme	Lymphohistiocytic meningitis with or without caseous necrosis. Tubercular granuloma with multinucleate giant cells
Varicella zoster	Meningitis with cerebellar ataxia	Vesicles with oral lesions	Multifocal vasculopathy, lymphocytes, and macrophages infiltrating the arterial media
Cryptococcosis	Chronic meningitis	Macules and nodules (in 10-15% of cases)	Meninges diffusely infiltrated with numerous cryptococci and mononuclear cells, occasional granulomatous reaction, and necrosis
Lymes disease	Aseptic meningitis, polyneuropathy, delayed demyelinating disease	Target lesion	Visible ependymal granulation, irregular nodular protrusions of subependymal glia. Leptomeninges show mild fibrosis and chronic infiltrate of lymphocytes
HIV	HIV-1-associated neurocognitive disorder (HAND), peripheral neuropathy, progressive multifocal encephalopathy, tuberculosis, toxoplasmosis, and infection with cytomegalovirus	Molluscum contagiosum, seborrheic dermatitis, verruca vulgaris, Kaposi sarcoma, herpes zoster	Multinucleated giant cells, microglial nodules/myelin loss
Neoplastic			
Leukemia	Meningeal leukemia is common form of relapse, seen in ALL	Erythema nodosum, Sweet syndrome	
Lymphoma, cutaneous (T cell)	Subacute meningitis, vertebral metastases	Scaly erythematous patches, leonine facies, poikiloderma, hypopigmented and hyperpigmented patches with atrophy and telangiectasia	

obstructive vasculopathy of small and medium-sized vessels, with variable degree of inflammation, sparing the tunica media.[2] Histological changes in the skin evolve in early, fully developed, and late lesions.[1] Based on the available evidence, various mechanisms have been proposed to explain the clinical manifestations of this disease including vasculitis, coagulopathy, and endothelial dysfunction triggered by viral or bacterial infections.[1] How the interplay of genetics, autoimmunity and coagulopathy drives the disease process and contributes to the obstructive vasculopathy of Degos disease still remains to be understood.

We highlight the clinical, radiological, and histological findings in a patient with systemic Degos disease and stress on meticulous skin examination as a crucial step in the diagnostic algorithm. It is important to establish an accurate diagnosis for counseling the patient regarding the prognosis. Knowledge gaps in the disease pathophysiology need to be filled so as to develop effective targeted therapies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Dodmallur Mallikarjuna Sindhu#, Sumanth Shivaram#, Shilpa Rao[1], Madhu Nagappa, Doniparthi V. Seshagiri, Vani Santosh[1], Madhukara J[2], Shreedhara AS[3], Maya D. Bhat[4], Rose D. Bharath[4], Sanjib Sinha

Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), [1]Department of Neuropathology, National Institute of Mental Health and Neurosciences (NIMHANS), [2]Department of Dermatology, St John's Medical College Hospital, [3]Department of Neurology, Columbia Asia Hospital, [4]Department of Neuroimaging and Interventional Radiology (NIIR), National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India
#Both authors have contributed equally.

Address for correspondence: Dr. Sanjib Sinha, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India.
E-mail: sanjib_sinha2004@yahoo.co.in

References

1. Theodoridis A, Makrantonaki E, Zouboulis CC. Malignant atrophic papulosis (Köhlmeier-Degos disease)-A review. Orphanet J Rare Dis 2013;8:10.
2. Amato C, Ferri R, Elia M, Cosentino F, Schepis C, Siragusa M, *et al*. Nervous system involvement in Degos disease. AJNR Am J Neuroradiol 2005;26:646-9.
3. Subbiah P, Wijdicks E, Muenter M, Carter J, Connolly S. Skin lesion with a fatal neurologic outcome (Degos' disease). Neurology 1996;46:636-40.
4. Ye L, Lekgabe E, Tsui A, Gaillard F. The evolution of cerebrovascular changes in Köhlmeier-Degos disease: An 11-year follow-up case report. J Clin Neurosci 2018;48:114-7.
5. Dastur DK, Singhal BS, Shroff HJ. CNS involvement in malignant atrophic papulosis (Kohlmeier-Degos disease): Vasculopathy and coagulopathy. J Neurol Neurosurg Psychiatry 1981;44:156-60.
6. Caviness Jr VS, Sagar P, Israel EJ, Mackool BT, Grabowski EF, Frosch MP. Case 38-2006: A 5-year-old boy with headache and abdominal pain. N Engl J Med 2006;355:2575-84.
7. Moss C, Wassmer E, Debelle G, Hackett S, Goodyear H, Malcomson R, *et al*. Degos disease: A new simulator of non-accidental injury. Dev Med Child Neurol 2009;51:647-50.
8. Yeo TH, Vassallo G, Judge M, Laycock N, Kelsey A, Crow YJ. Infantile neurological Degos disease. Eur J Paediatr Neurol 2011;15:167-70.
9. Matsuura F, Makino K, Fukushima T, Matsubara N, Shibuya M, Higuchi T, *et al*. Optic nerve and spinal cord manifestations of malignant atrophic papulosis (Degos disease). J Neurol Neurosurg Psychiatry 2006;77:260-2.
10. Sharma S, Brennan B, Naden R, Whelan P. A case of Degos disease in pregnancy. Obstet Med 2016;9:167-8.

Submitted: 19-Sep-2020 **Revised:** 24-Sep-2020 **Accepted:** 03-Nov-2020
Published: 27-Mar-2021

DOI: 10.4103/aian.AIAN_1004_20