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Radiological-Pathological Correlation

Degos disease: A radiological-pathological correlation of the neuroradiological aspects of the disease

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ABSTRACT

Malignant atrophic papulosis (Degos disease) is an unusual thrombotic microangiopathy of uncertain etiology. The disease characteristically involves the skin and internal organs, with nervous system involvement more common in children. We present a case with diverse neurological manifestations including cranial nerve palsies, gait instability, and urinary incontinence. The patient also developed white papular lesions on her lower extremities and back. Magnetic resonance imaging (MRI) demonstrated progressive intracranial and spinal abnormalities. Despite treatment with numerous biologic agents, the patient had persistent clinical deterioration and expired one month after admission. We highlight the extensive neurologic manifestations of Degos disease correlated with neuroradiological imaging and pathological features. Nervous system involvement in Degos disease requires careful neurologic and dermatologic exam with central nervous system (CNS) magnetic resonance imaging to distinguish it from non-organic etiologies of similar symptoms.

1. Introduction

Köhlmeier-Degos or Degos disease was first described in the 1940s. From 1941 to 1948, four cases of a condition that affected both the skin and the intestines, leading to peritonitis, were described in the literature under different interpretation [1-4]. In the first case, the emphasis was on thromboangiitis of the mesenteric vessels [1]. The subsequent case focused on the skin lesions [2]. With the report of additional cases [3,4], similarities were observed, and the disease process was interpreted as Degos disease. The main histopathology of these lesions is the presence of small vessel vasculopathy that may be seen in the different organs involved. It is important to highlight that the atrophic papulosis present in these cases may be separated into benign atrophic papulosis in patients with skin-only involvement, and malignant atrophic papulosis, when the process involves internal organs—more commonly the gastrointestinal system, and less commonly the renal system and nervous system [5]. Neurologic manifestations of Degos disease more commonly present as cranial nerve deficits and polyradiculoneuropathy. Neurologic involvement occurs in 20–60% of cases and is more common in children. In our experience, the patient initially presented with facial numbness and progressive neurologic symptoms, with eventual development of the classic rash. In this report, we will highlight the neurologic, radiologic, and pathologic manifestations of Degos disease.

2. Case presentation

2.1. Clinical features

A 15-year-old female with no significant past medical history initially presented with facial numbness that involved both sides of her face and conjunctiva, which was first noticed when patient had applied eyeliner into her eye. She was first evaluated for persistent facial numbness two months after initial symptoms, ten months prior to admission to our institution. A computed tomography (CT) head was done and found to be normal. She was then referred to neurology. The following month, she was admitted to a hospital with concern for progression of symptoms. MRI of the brain and cervical spine without contrast, as well as magnetic resonance angiography and venography (MRA and MRV) without contrast were normal. One month later her exam again showed facial numbness in an unclear nerve branch distribution. Six months into her presentation, her family noted appearance of a rash described as “whiteheads” predominantly over the lower extremities. Pictures of the rash resembled white papules with central umbilication and surrounding erythema. In addition to the rash, she developed difficultly controlling her oral secretions and visual changes such as light sensitivity with red, watery eyes. Evaluation by ophthalmology revealed absent corneal reflex. At this time, the patient also had

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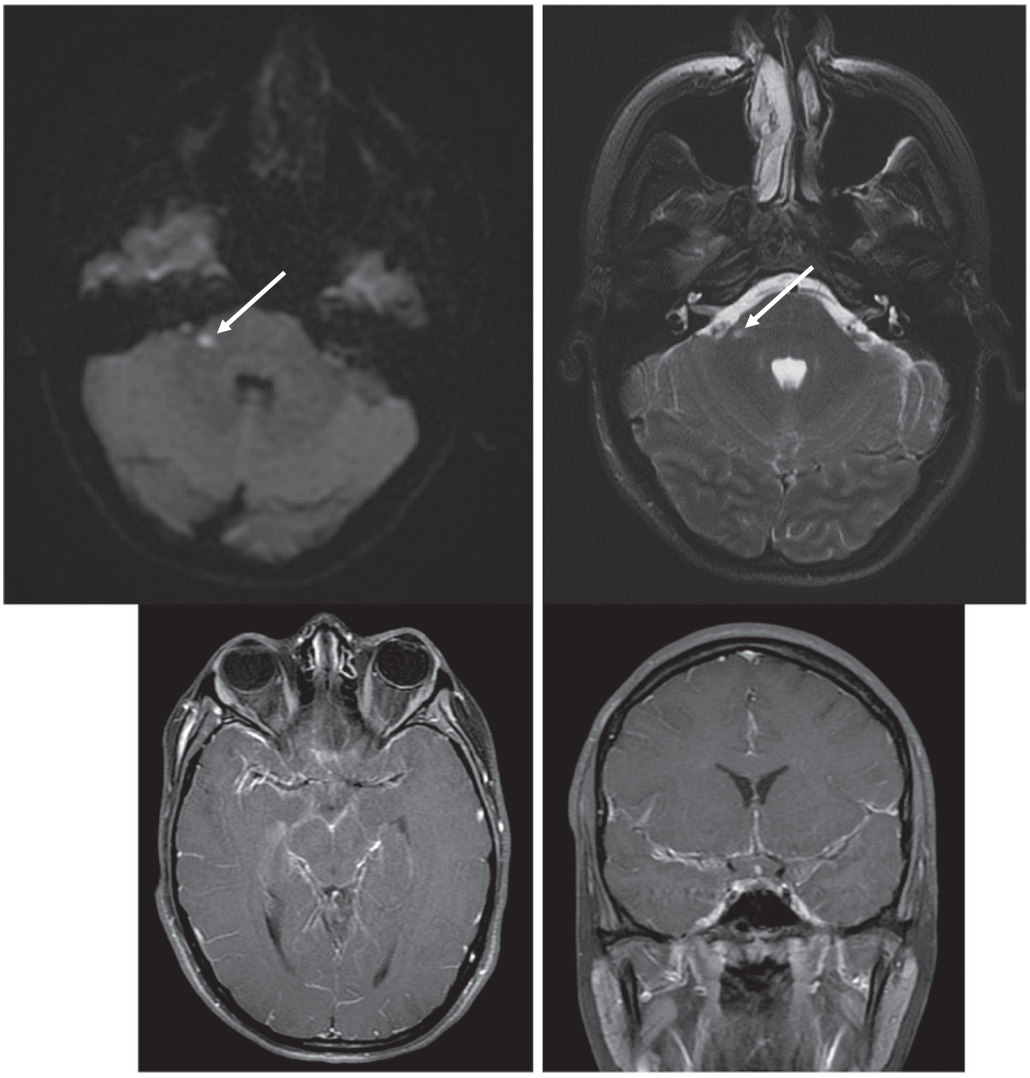

Fig. 1. MRI brain with and without contrast. Axial DWI (top left), Axial T2 (top right), Axial T1 post-contrast (bottom left) and Coronal T1 post-contrast (bottom right). Focal lesion with restricted diffusion with T2 signal abnormality in the right brachium pontis (arrow). Diffuse abnormal leptomeningeal enhancement within the basal cisterns and sylvian fissures. Images obtained 45 days prior to patient's fatal outcome.

progressive numbness of her face and bilateral legs from the knee down. MRI of the spine with and without contrast and electromyography were normal. Due to her continuous deterioration, further MRI of the brain and complete spine with and without intravenous contrast demonstrated diffuse avid leptomeningeal enhancement within the basal cisterns, sylvian fissures and scattered areas along the bilateral cerebral convexities. In addition the patient had developed a focus of T2 hyperintensity with diffusion restriction in the ventral right brachium pontis. Scattered foci of T2 hyperintensity within the peripheral spinal cord without enhancement, mild enhancement of the cauda equina and regions of leptomeningeal enhancement along the cord margin were also present.

2.2. Neurologic exam on admission

Neurologic exam was significant for cranial nerve (CN) III, IV, and VI palsies causing anisocoria, left-sided ptosis, and extraocular muscle limitations. Also notable was bilateral right end gaze nystagmus; mild flattening of the right nasal-labial fold with right facial weakness in an upper motor neuron distribution; and 3/5 strength, mild hyperreflexia, and mild loss of vibratory sensation throughout bilateral lower extremities. Strength was intact in bilateral upper extremities. Sensation deficits included T10 level and lower to light touch, and T8 level to pinprick. The patient was conscious and responsive throughout the examination, though somnolent, falling asleep at various times throughout history taking. Speech was mildly slowed and notable for mild dysarthria.

2.3. Further clinical evaluation

On admission, the skin rash was most notable on bilateral thighs, lower legs, and feet, though also appeared on her back, and bilateral

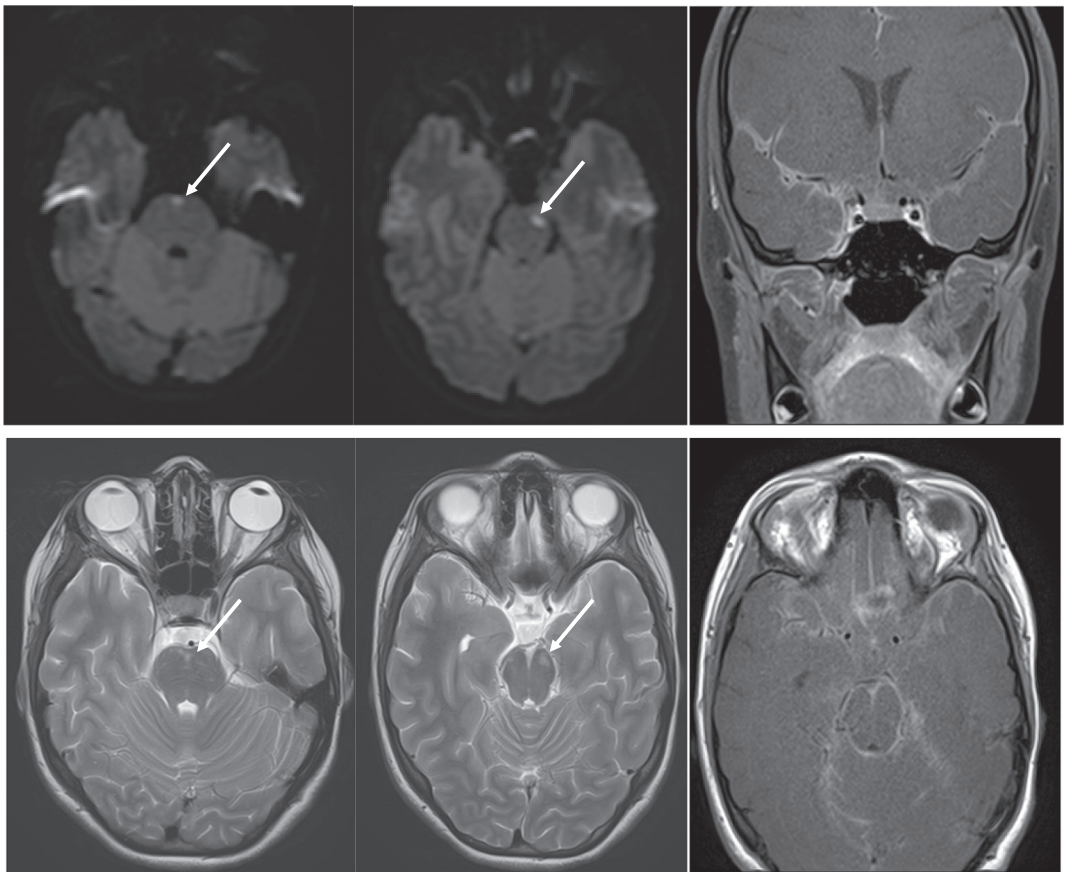

Fig. 2. MRI brain with and without contrast. Axial DWI (top left, top middle), Axial T2 (bottom left, bottom middle), Coronal T1 post-contrast (top right) and Axial T1 post-contrast (bottom left). Focal lesions with restricted diffusion within the midbrain and pons (arrow). Diffuse abnormal leptomeningeal enhancement within the basal cisterns and sylvian fissures. Images obtained 37 days prior to patient's fatal outcome (image obtained 8 days after Fig. 1).

arms mainly at the wrists. As described, the rash appeared as white papules with central umbilication and erythematous circumferential border. An extensive infectious and autoimmune workup including bacterial, viral, fungal, and immunologic studies was performed and was negative. Based on the characteristic rash and declining neurologic status despite immunosuppression, the diagnosis of Degos disease was given high consideration. Further evaluation of the skin biopsy was deemed to be highly compatible with Degos disease. A repeat MRI of the brain with and without contrast taken 8 days after the initial abnormal MRI showed progressive intracranial disease with multiple new foci of non-enhancing T2 signal and diffusion restriction especially along the margins of the brainstem with additional scattered cortical subcortical foci within the infra- and supratentorium (Figs. 1 and 2). Avid leptomeningeal enhancement was persistent. Repeat MRI of the complete spine with and without contrast revealed a new mildly expansile, non-enhancing T2 hyperintense lesion within the T6–T7 thoracic cord (Fig. 3). Also noted was cauda equina enhancement with mild leptomeningeal enhancement along the spinal cord. Throughout the remainder of the hospitalization, repeat MRIs of the brain showed development of multiple punctate regions on the brain surface with development of areas of diffusion restriction concerning for possible demyelination versus ischemia.

Despite aggressive treatments with Ruxolitinib and Tocilizumab, the patient succumbed to respiratory failure approximately one month after admission.

2.4. Pathological features

Histological sections of the brain and spinal cord show evolving intraparenchymal infarct areas (Fig. 4A–E). Also, secondary demyelination and collections of macrophages were present. In addition, areas of reactive gliosis and perivascular inflammation in the leptomeninges were identified.

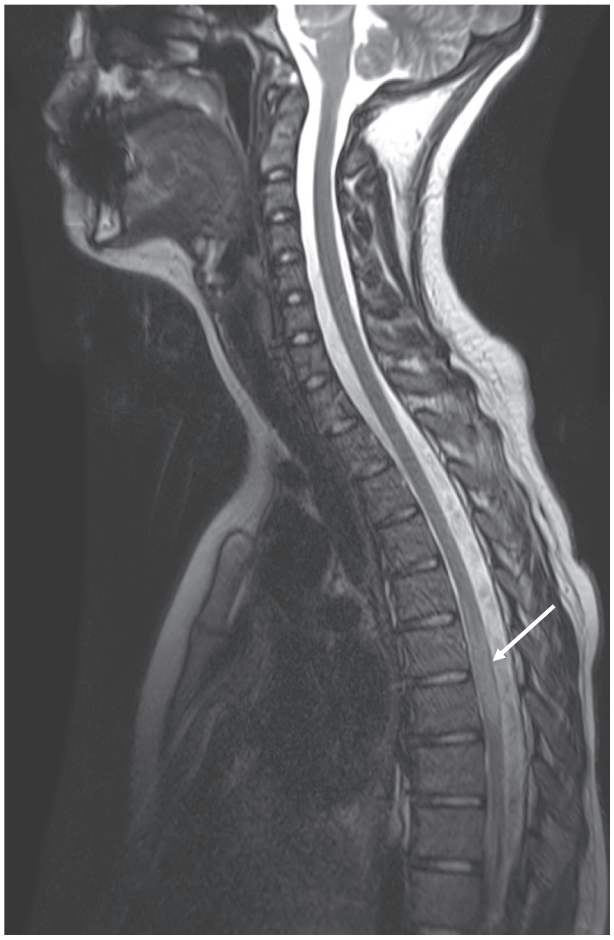

Fig. 3. MRI complete spine with and without contrast. Sagittal T2 image thru the cervicothoracic cord demonstrates mildly expansile T2 hyperintense lesion of the T6-T7 cord without associated enhancement (not shown). Image obtained 37 days prior to patient's fatal outcome.

3. Discussion

Degos disease has been defined as a papulosis atrophicans maligna, which is characterized by a thrombotic microangiopathy of uncertain etiology most often affecting the skin, gastrointestinal, and nervous systems. In addition to clinical findings, the diagnosis of Degos disease can be confirmed with skin biopsy. This disease appears to affect patients in a wide range of ages, with diagnosis documented in patients 2–64 years old [6]. Some authors have suggested the possibility of a familial origin in some cases, as the appearance of this disease in multiple family members has been well documented [7]. In that regard, Katz et al. [8] documented a case in which the disease appeared in three generations of the same family. In addition, Degos disease often appears to be accompanied by another underlying condition such as antiphospholipid antibody syndrome, systemic sclerosis, dermatomyositis, and systemic lupus erythematosus [9].

It is estimated that nervous system involvement ranges from 20 to 60% and is more common in the pediatric population [10,11], compared to gastrointestinal system involvement in approximately 50% of cases. Regarding the neurologic manifestations of Degos disease, different pathological features have been described. Dastur et al. [12] reported a 42-year-old man in whom mental dysfunction, paraesthesiae, weakness of the left limbs with pyramidal tract sign, bilateral ptosis, progression to total ophthalmoplegia, and obtundation were present; the patient followed a fatal course. At autopsy, the brain showed multiple small hemorrhagic infarcts in both hemispheres, the lower mid-brain, pons, and cerebellar peduncle. In addition, fibrin exudate in the leptomeninges with various stages of thrombosis of small arteries without inflammatory reaction, as well as acute and subacute microinfarcts was found. In a report of 15 patients with Degos disease, Subbiah et al. [13] identified 10 patients with neurologic manifestations including five patients who developed fatal hemorrhagic or ischemic strokes, one who showed polyradiculoneuropathy, and four with non-specific neurologic symptoms without objective findings. Amato et al. [14] also reported a 29-year old woman who developed peripheral and CNS involvement in the form of ischemic lesions, and diffuse and homogeneous thickening of the meninges with spinal MRI showing thinning of the spinal cord. Huang et al. [15] reported neurologic involvement in a 4-year-old girl whom on examination showed left ptosis, lateral deviation of the left eye, and mydriasis without light reflex. CT scan of the patient showed effusion in the frontoparietotemporal area of the bilateral hemispheres and several calcifications in the left cerebral cortex. Hu et al. [16] reported a 30-year-old woman who ultimately died of intestinal perforation, but who also developed motor aphasia with MRI brain showing small lesions in the left cerebral hemisphere suggestive of ischemic small vessel disease. Gmuca et al. [17] documented similar findings in their report of the autopsy findings of a 4-year-old boy in which the authors documented CNS vasculopathy with multiple foci of hemorrhage and infarction. Interestingly, Ye et al. [18] was able to document the cerebrovascular changes of a patient over a period of 11 years in which the authors documented progressive right sided cerebral arterial narrowing and ultimately occlusion of the right MCA branches. Based on both reported cases and our own experience, we consider that patients with Degos disease and evidence of CNS involvement are more likely to follow a fatal course, contrary to patients with Degos disease and non-specific peripheral nervous system or other organ involvement. The variable neurologic manifestations of Degos disease are included in the table (see Table 1 [12-18]).

More recently, Magro et al. [6] documented four cases of Degos disease in which the authors evaluated the expression of myxovirus resistance gene A (MXA)-specific antibody in tissue. Through immunofluorescent studies, the authors also evaluated the presence of C5b-9 as well as other immunoglobulins (Ig) including IgA, G, and M, fibrin, and C3 in tissue lesions. They also identified the presence of C5b-9 in the skin, gastrointestinal system, and brain, as well as high expression of MXA, which is a type I interferon-inducible protein. The authors concluded that dysregulated interferon-alpha response in concert with membranolytic attack complex deposition may contribute to

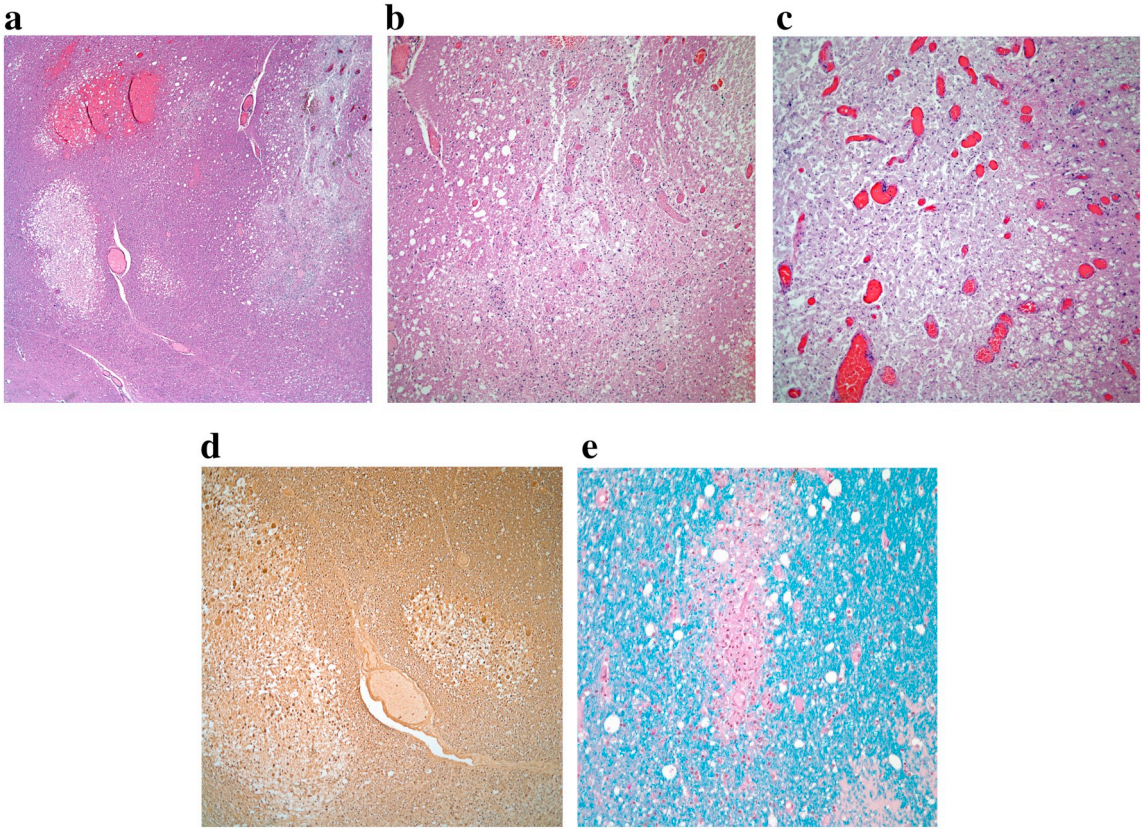

Fig. 4. A) Low power view of a brain section showing areas of infarct, B) collections of macrophages and mild inflammatory reaction, C) areas of infarct in the spinal cord, D) NFP immunostain (neurofilament protein), clearly demarcates the areas of infact, E) PAS histochemical stains highlights the presence of macrophages.

the vascular changes seen in the disease. Magro et al. [19] also recently suggested that the Rho kinase pathway activation may also be involved in cases of Kohlemeier-Degos disease. Eculizumab, a humanized monoclonal antibody, is a treatment that binds and inhibits Complement 5 (C5). Ruxolitinib, a Janus kinase inhibitor used in interferonopathies, was initiated in our patient as her skin biopsy findings showed increased MXA staining. The rational for treatment with both Treprostinil and Tocilizumab was to target angiogenic properties. Given the understanding that Degos disease may lead to a paucity of endothelial progenitor cells, Treprostinil was added to the treatment course, as it is thought to increase angiogenic potential of endothelial progenitor cells. Tocilizumab, an anti-IL6 agent, was added after careful evaluation of the benefit of potential antifibrotic properties. Despite these treatments, it is possible that the degree of fibro-occlusive lesions may have been extensive that irreversible damage had likely rendered her refractory to therapy.

In our experience, the overall constellation of findings in the brain and spine appeared to be consistent with the neurologic manifestations noted in Degos disease. The unique neurologic findings in the patient presented expand on what other authors have documented in previous cases involving the nervous system, and we posit that CNS involvement likely represents a poor outcome in these patients. Our patient developed a mildly expansile T2 hyperintense lesion in her spine that on autopsy was identified as evolving infarcts. To our knowledge, this is a rare occurrence in patients with Degos disease that has not been well defined in the literature. Similarly, cauda equina and extensive nerve root enhancement has not been previously reported in Degos disease. Our patient presented with multiple progressive cranial nerve palsies, which manifested as dysarthria, dysphagia, and ocular muscle deficits, as well as significant motor and sensory losses. Though cranial nerve involvement in patients with Degos disease has been described in the literature, the extent of our patient's involvement was remarkable.

In short, we report a 15-year-old female with unusual neurological findings, classical skin lesions, and interferon signature staining and complement activation on tissue biopsy. These findings together are consistent with the diagnosis of Degos disease. Severe neurological

Table 1
Clinical features of reported cases of Degos disease with CNS involvement.

Case	Age/sex	Initial clinical symptoms	CNS involvement	Imaging	Follow-up
Dastur et al.	42/M	Few papules over his body, leg paresthesias and hemiparesis	Impaired memory, dysarthria, left hemiparesis, bilateral pyramidal signs, nystagmus, bilateral ptosis	N/A	Deceased
Amato et al.	29/F	3-Year history of skin lesions, intense fatigue, paresthesias, diplopia, ataxic gait	Anisocoria, hearing loss, muscle hypotrophy, mild paresis, paralysis of both legs, hypoesthesia, hypopallesthesia	Ischemic lesions, thickening of the meninges	N/A
Huang et al.	4/F	Sudden onset of ptosis of the left eyelid, several porcelain-white atrophic papules on her trunk and thighs	Left ptosis, mydriasis. 10 days after admission-acute infarction in left frontal lobe	Effusion in the frontoparietal hemisphere, and calcifications in the left cerebral cortex	Deceased
Gmuca et al.	4/M	Headache, right subdural hygroma	Left hemiparesis, acute infarcts in the anterolateral right pons	Punctate infarcts in right hemisphere, irregularities in the Circle of Willis on angiogram suggestive of vasculitis	Deceased
Hu et al.	30/F	Abdominal pain and speech disorder, skin lesion on her body	Motor aphasia	Ischemic small vessel disease on cranial MRI	Deceased
Ye et al.	32/F	Transient left sided hemiplegia, negative for cutaneous lesions	Left upper and lower limb weakness	Narrowing of the middle cerebral artery on MRI	Alive
Subbiah et al.	18/F	Skin lesions	Parasthesias/weakness, headache, dizziness	CT Head-negative	Alive
	31/M	Neurologic symptoms	Parasthesia, dysarthria, left hemiplegia, gaze palsy, left facial palsy	CT Head-decreased signal right frontal region	Alive
	38/M	Skin lesions	Dizziness	N/A	Alive
	16/F	Skin lesions	Headache, parasthesias of extremity	N/A	Alive
	50/F	Skin lesions	Headache, nystagmus, papilledema, hyporeflexia	N/A	Deceased
	14/F	Skin lesions	Seizures, decreased memory paresthesia, dysarthria, left 3rd nerve palsy, hyperreflexia	CT Head-subdural hematoma/shift, decreased signal left frontal region	Deceased
	10/M	Skin lesions	Somnolence, paraplegia	CT Head-subdural hematomas	Deceased
	42/F	Skin lesions	Headache, paresthesia, hyporeflexia	N/A	Alive
	33/M	Skin lesions	Parasthesia, dysarthria, headache, right scotoma, left facial palsy, hemiparesis, paraplegia	N/A	Deceased

deficits that present in this condition require thorough examination of the brain and spine with contrast imaging. We suggest that appropriate imaging decreases the potential for misdiagnosis of neurologic involvement in Degos disease and stresses the need to keep this diagnosis on the differential.

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