Published in final edited form as:

J Am Acad Dermatol. 2016 December ; 75(6): 1274–1277. doi:10.1016/j.jaad.2016.09.015.

Diffuse atrophic papules and plaques, intermittent abdominal pain, paresthesias, and cardiac abnormalities in a 55-year-old woman

Brittany Oliver, BS^a, Manfred Boehm, MD^b, Douglas R. Rosing, MD^c, Lee S. Shapiro, MD^d, Daniel T. Dempsey, MD^e, Peter A. Merkel, MD^f, Chyi-Chia Richard Lee, MD^g, and Edward W. Cowen, MD, MHSc^h

^aNational Institutes of Health, Bethesda, MD

^bCenter for Molecular Medicine, National Heart, Lung, and Blood Institute, Bethesda, MD

^cNational Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

^dThe Center for Rheumatology, Saratoga Springs, NY

^eDepartment of Surgery, University of Pennsylvania, Philadelphia, PA

^fDivision of Rheumatology, University of Pennsylvania, Philadelphia, PA

^gLaboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

^hDermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Keywords

vasculopathy; malignant atrophic papulosis; Degos disease; ecilizumab; treprostinil; complement; interferon

CASE SUMMARY

History

A 55-year-old Caucasian woman was referred to the National Institutes of Health (NIH) for evaluation of widespread white papules and plaques, intermittent abdominal pain, cardiac abnormalities, and paresthesias. Symptoms began at age 50 years with painful skin lesions

Correspondence to: Edward W. Cowen, MD, MHSc, Dermatology Branch, Center for Cancer Research, National Cancer Institute, Bldg10/Room 12N238, 10 Center Dr., MSC 1908, Bethesda, MD 20892-1908. Phone: (301) 496-2481. Fax: (301) 496-5370. cowene@mail.nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest: No other potential conflicts of interest relevant to this article were reported.

on her extremities. Additional lesions later appeared on her chest, back, and abdomen over 3 – 4 months. Treatment with topical corticosteroids was initiated without benefit.

The following year, at age 51, the patient experienced new-onset severe, crampy abdominal pain. Abdominal computed tomography (CT) revealed evidence of small bowel inflammation. The pain subsided with bowel rest. She continued to experience occasional, mild abdominal pain for the next two years, during which time skin lesions improved in appearance but never resolved entirely.

At age 54, the patient's abdominal symptoms worsened with near-weekly severe bouts of pain for 2 – 3 months. Abdominal CT showed changes suggestive of inflammation in the duodenum and proximal jejunum with surrounding mesenteric fat stranding. Exploratory laparoscopy revealed widespread lesions on the surface of the liver, peritoneum, and large and small bowel; these were similar in appearance to the lesions on her skin.

This episodic abdominal pain was accompanied by the development of 10 – 20 painful new skin lesions and intermittent right-sided paresthesias of the arm and leg. Head and neck MRI were read as normal, failing to reveal any neurological defects. Electrocardiogram revealed asymptomatic atrial fibrillation; echocardiogram showed moderate tricuspid regurgitation deemed to be clinically insignificant. Already on daily 81 mg aspirin, the patient was additionally prescribed twice daily apixaban 5 mg and metoprolol 25 mg to reduce the risk of thromboembolic complications.

Family history was significant for cerebrovascular accidents in both parents. There was no family history of skin or gastrointestinal disease. Approximately 5 years after disease onset, the patient was seen in the NIH dermatology clinic for further assessment.

Physical Examination

Skin examination at the NIH showed numerous porcelain white, irregularly shaped, pinpoint to 6 – 8 mm atrophic papules on the body with sparing of the face and neck. A distinct rim of intense erythema with telangiectasias characterized all lesions. Smaller lesions were present on the thenar and hypothenar aspect of the palms. In several areas, including the abdomen, back, and proximal thighs, adjacent lesions formed larger atrophic plaques (Fig. 1). A dark red, irregular 4 mm papule with slight overlying scale was noted on the left medial knee.

Dermatopathology

Histopathologic examination of a skin punch biopsy specimen obtained from the left medial knee revealed focal lichenoid dermatitis with hyperkeratosis, thickened basement membrane, superficial and deep perivascular chronic inflammation, hemosiderin deposition, and increased dermal mucin (Fig. 2). No vascular immune complexes were seen on direct immunofluorescence.

Significant Diagnostic Studies

Laboratory studies were significant for the following: white blood cell count 3.04 K/ μ L (reference range, 3.98 – 10.04 K/ μ L), platelet count 165 K/ μ L (173 – 369 K/ μ L), and

absolute lymphocytes 0.71 (1.18 – 3.74 K/uL). Lupus anticoagulant, anti-nuclear antibody, anti-double-stranded DNA, and anti-extractable nuclear antigen panel were normal. IgM anti-cardiolipin antibody was 14 MPL (0 – 12 MPL); C3 and C4 complement were at the lower limit of normal. Tests for erythrocyte sedimentation rate, high-sensitivity C-reactive protein, fibrinogen, D-dimer, lactate dehydrogenase, immunoglobulins, and liver function were normal. Lipid panel was significant for total cholesterol of 229 mg/dL, LDL of 142 mg/dL, triglycerides of 212 mg/dL, and HDL of 45 mg/dL. PT, PTT, and INR were unremarkable with normal von Willebrand and Factor VIII activity. Electrocardiogram showed sinus rhythm and was within normal limits. Echocardiogram revealed a mildly dilated left atrium and the presence of atrial fibrillation. There was no evidence of pulmonary hypertension.

Diagnosis

Adult-onset malignant atrophic papulosis/systemic Degos disease (OMIM #602248).

Follow-up

After the patient's exploratory laparoscopy revealed widespread visceral involvement, intravenous eculizumab 990 mg weekly for four weeks followed by 1200 mg every other week was added to her ongoing drug regimen. At the time of her evaluation at NIH, the patient had been treated with eculizumab for 6 months. She reported resolution of abdominal symptoms within 2 weeks of initiation of eculizumab with the exception of an isolated episode of pain that occurred 5 months into treatment and resolved within 12 hours. There has been minimal formation of new skin lesions and no new cardiac or neurological symptoms have developed since eculizumab was initiated, although paresthesias still occur intermittently. The patient continues to be managed on daily aspirin, twice daily apixaban and metoprolol, and 1200 mg eculizumab twice monthly.

DISCUSSION

Malignant atrophic papulosis (MAP), also known as Degos disease, is a rare vasculopathy of small and medium-sized arteries affecting the skin that may progress to involve the gastrointestinal tract, central nervous system, heart, lungs, and eyes.^{1,2} Although the etiology of MAP is unclear, theories have implicated a viral pathogenesis, autoimmune dysfunction, and, more recently, dysregulation of interferon- α signaling and complement activation as mediators of endothelial damage.^{3,4} MAP is most often diagnosed in young to middle-aged Caucasian adults but may affect individuals of all ages and races.^{1,5} Rarely, familial occurrences have been reported.^{1,6–11}

The cutaneous findings of MAP are 2 – 15 mm rose-colored papules and plaques that evolve over several weeks, eventually healing to atrophic, porcelain-white papules surrounded by an inflamed, telangiectatic border.^{1,2} Lesions localize to the trunk and extremities, characteristically sparing the face and scalp.¹²

MAP limited to the skin is associated with a favorable long-term prognosis. Multi-organ involvement portends a poor prognosis with death often occurring within 2 – 3 years.² In this systemic form, cutaneous findings typically precede visceral disease by months to

years.¹⁻³ The gastrointestinal tract is the most frequently involved internal organ, and usually presents with acute, severe abdominal pain.^{2,6,13} The central nervous system is affected in approximately 20% of patients, with reported manifestations including paresthesias, headaches, hemiplegia, strokes, epilepsy, or nonspecific neurological symptoms.¹⁴ Common causes of death include sepsis from peritonitis and hemorrhagic or ischemic stroke.^{2,14}

While distinct cutaneous findings are a sensitive indicator of MAP, a thorough history and physical examination focused on abdominal, neurologic, and cardiac complaints is also warranted to capture evolution of systemic disease. Early detection of potentially lethal gastrointestinal involvement may be achieved via laparoscopy, thought to be a more sensitive diagnostic tool compared to endoscopy.¹⁵ Complete blood count, autoimmune profile, and coagulation studies may exclude other diagnoses. While no specific laboratory test can be used to diagnose MAP, correlating clinical features with suggestive histopathologic findings of lichenoid changes, increased dermal mucin, and perivascular lymphocytic infiltrate may aid in diagnosis.^{2,16}

Treatment of MAP has traditionally included antiplatelet (aspirin, dipyridamole) and anticoagulation (heparin, coumadin) therapy with minimal success. Other medications, including azathioprine, chloroquine, ethylestrenol, methotrexate, phenformin, stanozolol, and tacrolimus, have also been disappointing. Glucocorticoids are contraindicated and may worsen disease.^{2,3,16} Eculizumab, a monoclonal antibody which binds C5 complement, has led to dramatic responses in a small number of patients, possibly due to antiapoptotic endothelial effects.^{4,17,18} Results of recent use of eculizumab in combination with treprostinil, a prostacyclin analog that may enhance endothelial progenitor cells, are also encouraging.¹⁷ Early success with eculizumab supports complement activation as a potential driving mechanism of MAP, although reports of disease progression after initial response to the drug indicate additional factors at work in disease pathogenesis.^{17,18}

Acknowledgments

The research was supported by the Intramural Program of the National Institutes of Health (NIH), the Center for Cancer Research, the National Cancer Institute, and the Medical Research Scholars Program, a public-private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation, The American Association for Dental Research, The Howard Hughes Medical Institute, and the Colgate-Palmolive Company, as well as other private donors.

Dr. Merkel reports receiving research support from ChemoCentryx, Inc.

The authors would like to thank Jessica Caidor, RN, and Rebecca Huffstutler, CRNP of the National Heart, Lung, and Blood Institute at the National Institutes of Health for their contributions.

The patient is enrolled in the NIH Cardiovascular Disease Discovery Protocol ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01143454) NCT#01143454, protocol #10-H-0126) sponsored by the National Heart, Lung, and Blood Institute. Clinicians can refer interested patients to the NIH patient recruitment and referral office at 800-411-1222 or by e-mail at prpl@mail.cc.nih.gov.

ABBREVIATIONS USED

NIH	National Institutes of Health
CT	Computed tomography

MAP malignant atrophic papulosis

REFERENCES

1. Katz SK, Mudd LJ, Roenigk HH. Malignant atrophic papulosis (Degos' disease) involving three generations of a family. *J Am Acad Dermatol.* 1997; 37:480–484. [PubMed: 9308565]
2. Scheinfeld N. Malignant atrophic papulosis. *Clin Exp Dermatol.* 2007; 32:483–487. [PubMed: 17692056]
3. Heymann WR. Degos disease: Considerations for reclassification. *J Am Acad Dermatol.* 2009; 61:505–506. [PubMed: 19700015]
4. Magro CM, Poe JC, Kim C, Shapiro L, Nuovo G, Crow MK, et al. Degos disease: a C5b-9/ Interferon- α -mediated endotheliopathy syndrome. *Am J Clin Pathol.* 2011; 135(4):599–610. [PubMed: 21411783]
5. Barlow RJ, Heyl T, Simson IW, Schulz EJ. Malignant atrophic papulosis (Degos' disease) – diffuse involvement of brain and bowel in an African patient. *Br J Dermatol.* 1988; 118:117–123. [PubMed: 3342171]
6. Wilson J, Walling HW, Stone MS. Benign cutaneous Degos disease in a 16-year-old girl. *Pediatr Dermatol.* 2007; 24:18–24. [PubMed: 17300643]
7. Hall-Smith P. Malignant atrophic papulosis (Degos' disease): two cases occurring in the same family. *Br J Dermatol.* 1969; 81:817–822. [PubMed: 5359899]
8. Newton JA, Black MM. Familial malignant atrophic papulosis. *Clin Exp Dermatol.* 1984; 9:298–299. [PubMed: 6733962]
9. Moulin G, Barrut D, Franc MP, Perison A. Papulose atrophique de Degos familiale (mere-fille). *Ann Dermatol Venereol.* 1984; 111:149–155. [PubMed: 6721361]
10. Kisch LS, Bruynzeel DP. Six cases of malignant atrophic papulosis (Degos' disease) occurring in one family. *Br J Dermatol.* 1984; 111:469–471. [PubMed: 6487548]
11. Habbema L, Kisch LS, Starink ThM. Familial malignant atrophic papulosis (Degos' disease): additional evidence for heredity and a benign course. *Br J Dermatol.* 1986; 114:134–135. [PubMed: 3942684]
12. Degos R. Malignant atrophic papulosis. *Br J Dermatol.* 1979; 100:21–35. [PubMed: 371654]
13. Lankisch MR, Johst P, Scolapio JS, Fleming CR. Acute abdominal pain as a leading symptom for Degos' disease (malignant atrophic papulosis). *Am J Gastroenterol.* 1999; 94:1098–1099. [PubMed: 10201491]
14. Subbiah P, Wijdicks E, Muentner M, Carter J, Connolly S. Skin lesion with a fatal neurologic outcome (Degos' disease). *Neurology.* 1996; 46:636–640. [PubMed: 8618659]
15. Toledo AE, Shapiro LS, Farrell JF, Magro CM, Polito J. Laparoscopy shows superiority over endoscopy for early detection of malignant atrophic papulosis gastrointestinal complications: a case report and review of literature. *BMC Gastroenterol.* 2015; 15(156)
16. Ojeda Cuchillero RM, Sánchez Regaña M, Umberto Millet P. Benign cutaneous Degos' disease. *Clin Exp Dermatol.* 2003; 28:145–147. [PubMed: 12653699]
17. Shapiro LS, Toledo-Garcia AE, Farrell JF. Effective treatment of malignant atrophic papulosis (Köhlmeier-Degos disease) with treprostinil – early experience. *Orphanet J Rare Dis.* 2013; 8:52. [PubMed: 23557362]
18. Magro CM, Wang X, Garrett-Bakelma F, Laurence J, Shapiro LS, DeSancho MT. The effects of eculizumab on the pathology of malignant atrophic papulosis. *Orphanet J Rare Dis.* 2013; 8:185. [PubMed: 24279613]

KEY TEACHING POINTS

- Malignant atrophic papulosis (MAP) is a rare vasculopathy that may cause isolated cutaneous disease or severe, widespread disease involving the skin, gastrointestinal tract, central nervous system, and cardiovascular system.
- Early skin lesions of MAP appear as multiple rose-colored papules that evolve over several weeks to form a scar with an atrophic, porcelain-white center surrounded by an inflamed, telangiectatic border.
- Traditional therapeutic approaches appear to be ineffective, but new drugs, including eculizumab and treprostinil, have shown benefit in a small number of patients.

Figure 1. Malignant atrophic papulosis. (A) Porcelain white, irregularly shaped atrophic papules and plaques with erythematous, telangiectatic rim on the abdomen. (B) Close-up view of atrophic papules.

Figure 2. Dermatopathology of malignant atrophic papulosis. Lichenoid dermatitis with hyperkeratosis, patchy lymphocytic infiltrate, hemosiderin deposition, increased dermal mucin, and colloid bodies in the superficial dermis. (A) H&E, ×40; (B) H&E, ×400).