Malakoplakia in Thoracic Transplant Recipients

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ABSTRACT

Malakoplakia is a rare granulomatous disease characterized by the presence of Michaelis-Gutmann bodies on histopathologic analysis. Lesions manifest in a wide range of organs with cutaneous, gastrointestinal, and genitourinary systems being most common, and often result in significant comorbidities owing largely to misdiagnoses and the similar appearance to malignancy or granulomatous processes. Most patients are immunocompromised, including the solid-organ transplant population. Among organ recipients, malakoplakia is most commonly seen in renal transplantation, and only rarely reported in thoracic organ recipients. Herein we report 2 cases of malakoplakia in thoracic transplant patients that highlight the critical need for tissue diagnosis to avoid delay in management.

MALAKOPLAKIA is a rare pathologic diagnosis secured by the presence of Michaelis-Gutmann bodies on histology and can manifest as inflammatory plaques, nodules, and/or ulcers in multiple organs. Diagnosis is often delayed secondary to lesions mimicking other conditions, particularly malignancy. The pathogenesis is linked to abnormal innate immune responses toward bacterial pathogens, most frequently Gram-negative bacteria. It is most common in immunocompromised individuals, including solid-organ transplant patients. Malakoplakia has been described in renal transplant recipients, but is rarely seen in thoracic transplantation. Herein we report 2 cases in thoracic transplant recipients and review the literature.

CASE 1

A 67-year-old man, who underwent bilateral lung transplant for idiopathic pulmonary fibrosis, presented with perianal ulceration 17 months later. Before transplant he required bridging therapy with venovenous extracorporeal membrane oxygenation (VV-ECMO). Initial posttransplant medications included tacrolimus, mycophenolate mofetil, prednisone, atovaquone, and valganciclovir (cytomegalovirus donor-positive/recipient-negative [CMV D^+/R^-]).

At 9 months posttransplant, he received 3 doses of methylprednisone in the context of a new pleural effusion, which was originally thought to represent rejection, but was subsequently identified as a *Candida* empyema requiring decortication and prolonged fluconazole. Steroids were rapidly tapered to baseline and mycophenolate mofetil was discontinued secondary to his fungal infection. Ten months after transplantation, perianal lesions developed, thought to be hemorrhoids. In response to an increase in size of the lesions, he was empirically treated for herpes simplex infection, without improvement.

The lack of resolution prompted collection of anal biopsies that revealed dermal histiocytic infiltrate with chronic inflammation and fibrosis. Grocott methenamine silver (GMS) stain suggested blastomycosis based on morphology of yeast forms, an unexpected result given negative chest computed tomography (CT), sputum cultures, and serum fungal markers. Histoplasma urinary antigen, serum cryptococcal antigen, and blastomyces serum antibody returned negative results. Repeat biopsies revealed dense macrophage infiltration with cytoplasmic calcific inclusions in keeping with Michaelis-Gutmann bodies with a similar appearance to fungal organisms, consistent with malakoplakia (Fig 1A–D). Wound cultures grew *Escherichia coli*, *Klebsiella pneumoniae*, and rare alpha hemolytic *Streptococcus*, with no evidence of fungal pathogens. Immunosuppression was tapered with subsequent resolution of lesions.

CASE 2

A 56-year-old diabetic man underwent an orthotopic cardiac transplant for ischemic cardiomyopathy. The pretransplant course was complicated by lower extremity ischemia requiring bilateral transmetatarsal amputations secondary to bridging therapy with a left ventricular assist device. Posttransplant complications included a sacral decubitus ulcer and allograft rejection noted on right ventricle biopsy requiring treatment with antithymocyte globulin,

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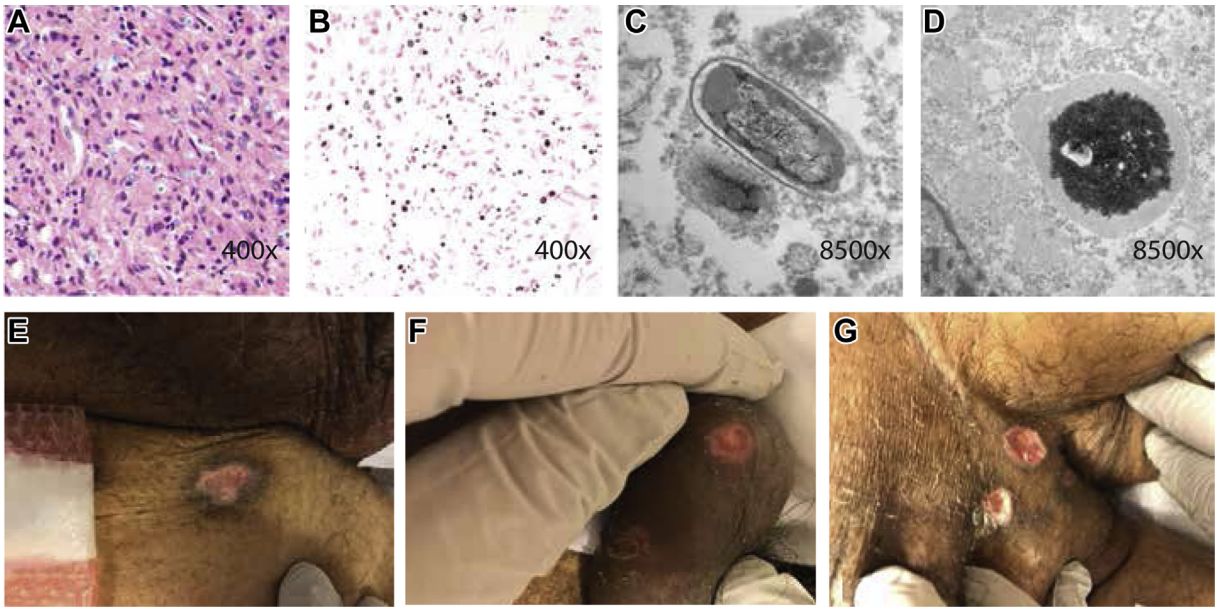

Fig 1. Gross image, histology, and ultrastructural appearance of malakoplakia lesions. Sheets of epithelioid macrophages, many of which contain small intracytoplasmic inclusions (Michaelis-Gutman bodies) (**A**). Von Kossa histochemical stain highlights the calcified cytoplasmic inclusions (**B**). Ultrastructure demonstrates bacillary forms consistent with the *E coli* (**C**), and ultrastructure shows a calcified lysosomal structure consistent with a Michaelis-Gutman body (**D**). Gross images of malakoplakia lesions from right upper thigh (**E**), penis (**F**), and scrotum (**G**).

plasmapheresis, and rituximab. Medications included tacrolimus, mycophenolate mofetil, prednisone, atovaquone, and valganciclovir (CMV D^+/R^+). Persistent low-grade (1A/1R) rejection led to a delayed taper of steroid therapy.

Four months after transplant, multiple painless ulcers involving thighs, scrotum, and penis evolved (Fig 1E–G). At this time, he was continuing to taper prednisone as per our institutional protocol. Work-up included negative urine *Chlamydia trachomatis* and *Neisseria gonorrhea* nucleic acid detection, human immunodeficiency virus (HIV) antibody/antigen, treponemal antibody, cryptococcal antigen, and swabs for herpes simplex virus antigen. Skin cultures revealed *E coli*, *Enterococcus faecalis*, *Staphylococcus haemolyticus*, moderate *Proteus mirabilis*, and rare *K pneumoniae*. Fungal and mycobacterial cultures were negative. Biopsies revealed acute and chronic dermal inflammation with necrosis, with Brown-Hopps stain positive for bacterial aggregates. Additional studies, including GMS, Giemsa, Fite special stain, and spirochete immunostains, were negative. Despite prolonged antimicrobial courses of amoxicillin-clavulanate and doxycycline, the genitourinary lesions remained unchanged over 2 months.

The patient presented again with acute right groin pain 6 months after transplant. Physical exam, ultrasound, and CT imaging confirmed a 3.2-cm inguinal lymph node. Blood cultures were positive for *E coli* and *S epidermidis*. Amoxicillin-clavulanate was changed to vancomycin and piperacillin-tazobactam, with continued doxycycline. Lymph node excision and skin biopsies revealed sheets of histocytes with acute abscess formation. Von Kossa special stain for calcium confirmed Michaelis-Gutmann bodies, consistent with malakoplakia. Treatment was narrowed to ceftriaxone with initial improvement but worsened in the context of treatment for subsequent cardiac rejection and intensification of his immunosuppressive regimen. At 12 months posttransplant, lesions had resolved with the formation of keloid scars.

LITERATURE REVIEW

We performed a PubMed literature search using the mapped term "malakoplakia" in addition to the stems "malakoplak" and "malacoplak," limited to thoracic organ transplantation. Cases were limited to those published in English. Of 966 cases reviewed, 2 additional [1,2] thoracic transplant cases were found (Table 1).

These 4 cases show an age range of 42–67 years, with a male predominance of 75%. None of these thoracic transplant cases had classic involvement of the urinary tract, instead perineal and gastrointestinal involvement with regional lymphadenopathy were most typical. *E coli* was identified as the most frequent organism, although in some cases the causative organism was not always clear. Despite literature reporting frequent surgical debridement as primary management, it was not required in these cases. Targeted antibiotic therapy ranged from 3 to 12 weeks. One case resolved with reduction in immunosuppression alone.

DISCUSSION

Malakoplakia, derived from the Greek *malakos* (soft) and *plakos* (plaque), is a histologic diagnosis seen commonly, but not exclusively, with the pathognomonic Michaelis-Gutmann bodies. Michaelis-Gutmann bodies consist of foamy macrophages showing "targetoid" basophilic intracytoplasmic inclusions, which have undergone progressive mineralization likely related to calcification of the lysosome. Macroscopically it presents as yellow-tan plaques or nodules [3].

Table 1. Review of Known Cases With Malakoplakia in Thoracic Transplant Recipients

Reference	Case (Years)	Underlying Transplanted Organ	Location	Organism	Comment	Treatment	Outcome	Differential Diagnosis
Case 1	55M	Heart	Perineal ulcer with regional lymph nodes	*Escherichia coli*, *Staphylococcus epidermidis*		Ceftriaxone 1 g IV for 21 days; doxycycline 100 mg orally twice daily for 21 days; vancomycin IV for 14 days	Cure	Sexually transmitted genitourinary ulcers
Case 2	67M	Lung	Perirectal ulcers and rectal mass	*E coli*		Reduction in immunosuppression	Cure	Invasive blastomycosis
Colby et al [1]	42M	Heart	Pulmonary nodule	Unclear–possible organisms include *Corynebacterium* spp, *Acinetobacter* spp, *Cryptococcus*, or *Staphylococcus* spp	Lost to follow-up while on treatment; final admission also presented with possible cerebral lymphoma	Ampicillin for 3 months, erythromycin for unclear duration (loss to follow-up), amphotericin B and 5FC for 14 days until death	Death	Not documented
Teeters et al [2]	55F	Heart	Perineal ulcers and rectal mass with regional lymph nodes	*E coli*	Diabetes	Ciprofloxacin IV, then oral for 10 weeks	Cure	Rectal cancer

Abbreviations: F, female; IV, intravenous; M, male.

Microscopic features are progressive with early lesions showing plaquelike induration followed by ulceration and granulomatous inflammation with sheets of epithelioid histocytes, which may later calcify and fibrose [3].

As in these cases, the major risk factors include immune dysregulation such HIV infection, diabetes mellitus, alcohol, and use of immunosuppression, although presentations in apparently immunocompetent individuals have been reported [4,5].

Both of our cases highlight a critical difficulty, namely the delay and misdiagnosis of malakoplakia for indolent infections or malignancy. Complicating the diagnosis is the association of malakoplakia with coexistent malignancy, particularly adenocarcinoma of the colon and rectum [6], primary lymphomas of the bladder [7], and squamous cell and papillary urothelial cancers of the renal tract and prostate [8,9]. Unlike this series in thoracic recipients, the genitourinary tract is the most common presenting location, although other sites of involvement include the tongue, colon, stomach, lung, trachea, liver, bone, thyroid, and uterus [3]. In genitourinary tract disease, 40% occurs within the bladder, with a female preponderance (ratio of 4:1) reported [3]. These cases demonstrate the critical need for considering malakoplakia in the differential diagnosis, especially in immunocompromised patients.

The pathogenesis of malakoplakia is thought to involve a defect in innate immune catabolic responses after ingestion or phagocytosis of bacteria within phagolysosomes. Many mediators have been implicated, such as low intracellular cyclic guanosine monophosphate (cGMP) levels, particularly in ratio to cyclic-adenosine monophosphate (cAMP), which result in defective microtubule function.

Similar to our cases, the association of malakoplakia with particular organisms suggests a pathogen-specific abnormal innate immune response. *E coli* is the most common agent, although other Gram-negative and positive organisms have been implicated. *Rhodococcus equi*, a Gram-positive coccibacillus, has been associated with pulmonary malakoplakia, particularly in those with HIV infection, as well as transplant recipients [10]. Other associated pathogens include mycobacteria, *Staphylococcus aureus*, *Pasturella multocida*, *Stenotrophomonas maltophilia*, Whipple disease, and syphilis [3,11–15]. In addition, concomitant infections with nonbacterial agents, including *Candida albicans*, *Paracoccidioides brasiliensis*, parasites such as *Taenia* species, and viruses, such as HSV and human papillomavirus, have been described [3,12,15–18]. Given that phagocytosis appears to be central to the pathogenesis, both host and microbial factors warrant further investigation for the identification of specific molecular mechanisms linking innate immune responses and pathogen recognition in malakoplakia.

Although classical pathologic changes are seen within tissue macrophages, abnormal inclusions have also been seen within circulating monocytes [19,20]. These observations imply a more systemic immune dysfunction beyond variables localized directly to tissue infection. There are no

clear associations with particular immunosuppressant medications to explain the phagocytic defect in malakoplakia, although it has been postulated that rates have decreased in the modern era of targeted T-cell therapies in transplantation such as tacrolimus and mycophenolate, rather than prednisone [21]. Interestingly, although one of our cases was on a delayed taper of steroids due to persistent low-grade rejection, and the other had received a pulse dose before presumed rejection, neither were on high doses at the time of lesion onset and were being tapered as per our institutional protocol. In a recent review of 40 cases of malakoplakia in kidney transplant recipients, events occurred at a median of 24 months posttransplant [16]. The thoracic cases described here occurred with a similar duration posttransplant, ranging from 4 to 17 months after thoracic organ transplantation.

Management involves the combination of prolonged antibacterial treatment targeting causative organisms, reduction in immunosuppression, and surgery. Protracted courses can result from cases in which ongoing immunosuppression is required, particularly in cases of allograft rejection requiring higher intensity immunosuppression. Use of bethanechol, a cholinergic agonist, and ascorbic acid have been utilized to alter the cGMP/cAMP ratios, improve microtubule function and promote phagocytosis, with some success in healing malakoplakia lesions [17,20,22].

These cases highlight malakoplakia as a diagnosis in the context of thoracic transplantation, although this observation may represent reporting bias. Despite thoracic transplant procedures occurring less frequently as compared with liver or renal transplantation, thoracic recipients likely carry a higher risk of infection owing to complex mechanical and anatomic defects. In addition, unlike abdominal transplantation, where blood biomarkers indicate the need for invasive biopsy (liver tests and creatinine), thoracic organ recipients often follow routine biopsy schedules that may reveal low-level rejection well before clinical symptomatology. This clinical approach may tend to place thoracic allograft recipients on more intensified immunosuppression, in turn resulting in more complex clinical manifestations of malakoplakia. Overall, further investigations of malakoplakia in the thoracic transplant population are warranted, especially as the numbers of thoracic recipients increase.

In conclusion, malakoplakia appears to be a rare, systemic disorder typically seen in immunocompromised patients, including thoracic transplant recipients. The chronicity of the lesions and resemblance to other critical processes, such as fungal infection or malignancy, emphasize the need for rapid biopsy diagnosis to avoid unnecessary diagnostics and the delay of appropriate therapy.

REFERENCES

[1] Colby TV, Hunt S, Pelzmann K, Carrington CB. Malakoplakia of the lung: a report of two cases. Respir Int Rev Thorac Dis 1980;39:295–9.

[2] Teeters JC, Betts R, Ryan C, Huether J, Elias K, Hartmann D, et al. Rectal and cutaneous malakoplakia in an orthotopic cardiac transplant recipient. J Heart Lung Transplant 2007;26:411–3.

[3] Yousef GM, Naghibi B, Hamodat MM. Malakoplakia outside the urinary tract. Arch Pathol Lab Med 2007;131:297–300.

[4] Shawaf AZ, Boushi LA, Douri TH. Perianal cutaneous malakoplakia in an immunocompetent patient. Dermatol Online J 2010;16:10.

[5] Goyal S, Parihar A, Puri V, Sharma N, Goyal A, Arora VK. An unusual large abdominal malakoplakia following trauma: diagnosed on FNAC. Diagn Cytopathol 2015;43:490–4.

[6] McClure J. Malakoplakia of the gastrointestinal tract. Postgrad Med J 1981;57:95–103.

[7] Matsuda I, Zozumi M, Tsuchida YA, Kimura N, Liu NN, Fujimori Y, et al. Primary extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type with malakoplakia in the urinary bladder: a case report. Int J Clin Exper Pathol 2014;7:5280–4.

[8] Lee SL, Teo JK, Lim SK, Salkade HP, Mancer K. Coexistence of malakoplakia and papillary urothelial carcinoma of the urinary bladder. Int J Surg Pathol 2015;23:575–8.

[9] Ngadiman S, Hoda SA, Campbell WG, Gardner T, May M. Concurrent malakoplakia and primary squamous cell carcinoma arising in long-standing chronic cystitis. Br J Urol 1994;74:801–2.

[10] Yamshchikov AV, Schuetz A, Lyon GM. *Rhodococcus equi* infection. Lancet Infect Dis 2010;10:350–9.

[11] Cachia AR, Eshoo S, Kench J, Fung C, Jones A, Iredell J, et al. Synchronous malakoplakia and Whipple's disease. Pathology 2005;37:315–7.

[12] Kradin RL, Sheldon TA, Nielsen P, Selig M, Hunt J. Malacoplakia of the tongue complicating the site of irradiation for squamous cell carcinoma with review of the literature. Ann Diagn Pathol 2012;16:214–8.

[13] Chitasombat MN, Wattanatranon D. Disseminated *Mycobacterium simiae* with pelvic malakoplakia in an AIDS patient. Clin Med Insight Case Rep 2015;8:89–91.

[14] Botros N, Yan SR, Wanless IR. Malakoplakia of liver: report of two cases. Pathol Res Pract 2014;210:459–62.

[15] Rocha N, Suguiama EH, Maia D, Costa H, Coelho KI, Franco M. Intestinal malakoplakia associated with paracoccidiodomycosis: a new association. Histopathology 1997;30:79–83.

[16] Nieto-Rios JF, Ramirez I, Zuluaga-Quintero M, Serna-Higuita LM, Gaviria-Gil F, Velez-Hoyos A. Malakoplakia after kidney transplantation: case report and literature review. Transplant Infect Dis 2017;19.

[17] Fudaba H, Ooba H, Abe T, Kamida T, Wakabayashi Y, Nagatomi H, et al. An adult case of cerebral malakoplakia successfully cured by treatment with antibiotics, bethanechol and ascorbic acid. J Neurol Sci 2014;342:192–6.

[18] Yang YL, Xie YC, Li XL, Guo J, Sun T, Tang J. Malakoplakia of the esophagus caused by human papillomavirus infection. World J Gastroenterol 2012;18:6690–2.

[19] van Crevel R, Curfs J, van der Ven AJ, Assmann K, Meis JF, van der Meer JW. Functional and morphological monocyte abnormalities in a patient with malakoplakia. Am J Med 1998;105:74–7.

[20] Abdou NI, NaPombejara C, Sagawa A, Ragland C, Stechschulte DJ, Nilsson U, et al. Malakoplakia: evidence for monocyte lysosomal abnormality correctable by cholinergic agonist in vitro and in vivo. N Engl J Med 1977;297:1413–9.

[21] Leao CA, Duarte MI, Gamba C, Ramos JF, Rossi F, Galvao MM, et al. Malakoplakia after renal transplantation in the current era of immunosuppressive therapy: case report and literature review. Transplant Infect Dis 2012;14:E137–41.

[22] Curran FT. Malakoplakia of the bladder. Br J Urol 1987;59:559–63.