

Bullous Pemphigoid Associated With a Lymphoepithelial Cyst of the Pancreas

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PRACTICE POINTS

- Recalcitrant bullous pemphigoid has been associated with benign and malignant tumors.
- If clinically indicated, laboratory studies should be performed to evaluate a possible neoplastic process.

Bullous pemphigoid (BP) is an acquired, autoimmune, subepidermal blistering disorder. A possible paraneoplastic association has been suggested; however, debate remains regarding the precise relationship of these neoplasms with BP. We present a case of recalcitrant BP in a 67-year-old man with a pancreatic neoplasm that was found to be a lymphoepithelial cyst. Immunoperoxidase staining of the cyst demonstrated C3d along the basement membrane of the stratified squamous epithelium, suggesting that the BP may have involved the lymphoepithelial cyst itself. Shortly after excision of the cyst, BP rapidly resolved without any immunosuppressive treatment, raising the possibility that the

immunologic process involving the lymphoepithelial cyst of the pancreas was the inciting factor for the patient's cutaneous disease. Although rare, some cases of BP may be a paraneoplastic process. A thorough screening via patient history and directed laboratory studies may be warranted in recalcitrant cases.

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Bullous pemphigoid (BP) is an acquired, autoimmune, subepidermal blistering disease that is more common in elderly patients.¹ An association with internal neoplasms and BP has been established; however, there is debate regarding the precise nature of the relationship.² Several gastrointestinal tract tumors have been associated with BP, including adenocarcinoma of the colon, adenosquamous cell carcinoma and adenocarcinoma of the stomach, adenocarcinoma of the rectum, and liver and bile duct malignancies.³⁻⁵ Association with pancreatic neoplasms (eg, carcinoma of the pancreas) rarely has been reported.⁵⁻⁷ We present an unusual case of a lymphoepithelial cyst of the pancreas in a patient with BP.

Case Report

A 67-year-old man presented with erythematous crusted plaques and pink scars over the chest, back, arms, and legs (Figure 1). A 1.5-cm tense bullous lesion was observed on the right knee. The patient's medical history was

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The authors report no conflict of interest.

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notable for biopsy-proven BP of 8 months' duration as well as diabetes mellitus and hypothyroidism. The patient was being followed by his surgeon for a 1.9-cm soft-tissue lesion in the pancreatic tail and was awaiting surgical excision at the time of the current presentation. The pancreatic lesion was discovered incidentally on magnetic resonance imaging performed following urologic concerns. At the current presentation, the patient's medications included nifedipine, hydralazine, metoprolol, torsemide, aspirin, levothyroxine, atorvastatin, insulin lispro, and insulin glargine. He had previously been treated for BP with prednisone at a maximum dosage of 60 mg daily, clobetasol propionate cream 0.05%, and mupirocin ointment 2% without improvement. Because of substantial weight

gain and poorly controlled diabetes, prednisone was discontinued.

Bullous pemphigoid had been diagnosed histopathologically by a prior dermatologist. Hematoxylin and eosin staining demonstrated a subepidermal separation with eosinophils within the perivascular infiltrate (Figure 2). Direct immunofluorescence was noted in a linear pattern at the dermoepidermal junction with IgG and C3. Bullous pemphigoid antigen antibodies 1 and 2 were obtained via enzyme-linked immunosorbent assay with a positive BP-1 antigen antibody of 19 U/mL (positive, >15 U/mL) and a normal BP-2 antigen antibody of less than 9 U/mL (reference range, <9 U/mL). The glucagon level was elevated at 245 pg/mL (reference range, ≤134 pg/mL).



Figure 1. Erythematous crusted plaques on the chest and arms in a patient with bullous pemphigoid.

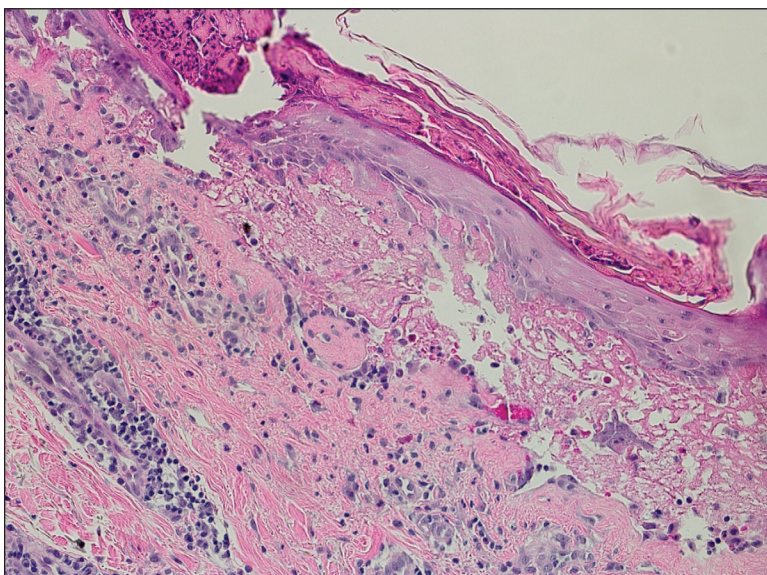


Figure 2. Subepidermal separation of the dermis and epidermis associated with eosinophils with a mild perivascular lymphocytic infiltrate consistent with bullous pemphigoid (H&E, magnification approximately ×100 by digital system).

The patient was prescribed minocycline 100 mg twice daily and niacinamide 500 mg 3 times daily. Topical treatment with clobetasol and mupirocin was continued. One month later, the patient returned with an increase in disease activity. Changes to his therapeutic regimen were deferred until after excision of the pancreatic lesion based on the decision not to start immunosuppressive therapy until the precise nature of the pancreatic lesion was determined.

The patient underwent excision of the pancreatic lesion approximately 3 months later, which proved to be a benign lymphoepithelial cyst of the

pancreas. Histology of the cyst consisted of dense fibrous tissue with a squamous epithelial lining focally infiltrated by lymphocytes (Figure 3A). Immunoperoxidase staining of the cyst revealed focal linear areas of C3d staining along the basement membrane of the stratified squamous epithelium (Figure 3B).

The patient stated that his skin started to improve virtually immediately following the excision without systemic treatment for BP. On follow-up examination 3 weeks postoperatively, no bullae were observed and there was a notable decrease in erythematous crusted plaques (Figure 4).

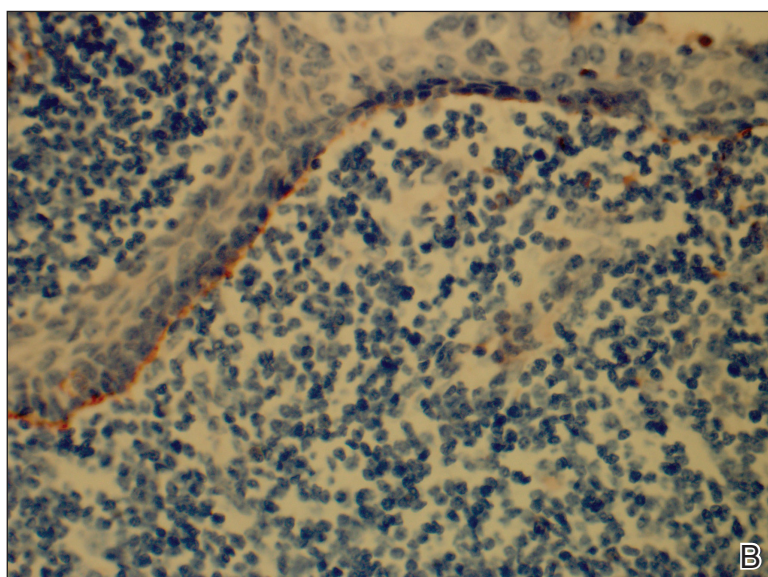
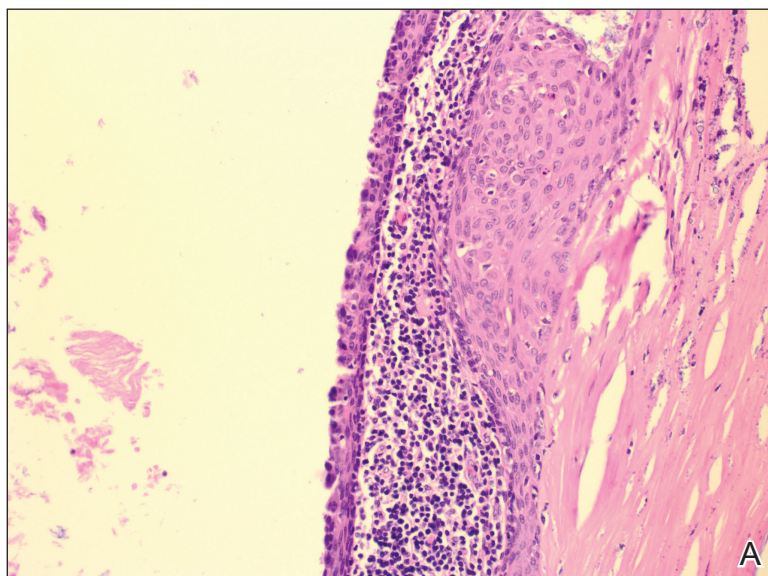


Figure 3. Histopathology of the lymphoepithelial cyst of the pancreas revealed squamous epithelial lining with no malignant features. A prominent lymphocytic component abutting the squamous epithelial lining was observed, which is characteristic of lymphoepithelial cysts of the pancreas (A)(H&E, magnification approximately $\times 100$ by digital system). Immunoperoxidase staining of the cyst revealing focal linear areas of C3d staining along the basement membrane of the stratified squamous epithelium (B) (magnification approximately $\times 400$ by digital system).



Figure 4. Three weeks following the surgical removal of the pancreatic lymphoepithelial cyst, pink and hypopigmented scars were noted in the same distribution as the previously active bullous pemphigoid lesions.

Comment

Paraneoplastic BP has been documented; however, lymphoepithelial cysts of the pancreas in association with BP are rare. We propose that the lymphoepithelial cyst of the pancreas provided the immunologic stimulus for the development of cutaneous BP based on the observation that our patient's condition remarkably improved with resection of the tumor.

There are fewer than 100 cases of lymphoepithelial cysts of the pancreas reported in the literature.⁸ The histologic appearance is consistent with a true cyst exhibiting a well-differentiated stratified squamous epithelium, often with keratinization, surrounded by lymphoid tissue. These tumors are most commonly seen in middle-aged men and are frequently found incidentally,⁸⁻¹⁰ as was the case with our patient. Although histologically similar, lymphoepithelial cysts of the pancreas are considered distinct from lymphoepithelial cysts of the parotid gland or head and neck region.¹⁰ Lymphoepithelial cysts of the pancreas are unrelated to elevated glucagon levels; it is likely that our patient's glucagon levels were associated with his history of diabetes.¹¹

The diagnosis of BP is characteristically confirmed by direct immunofluorescence. Although it was performed for our patient's cutaneous lesions, it was not obtained for the lymphoepithelial cyst of the pancreas. Once the diagnosis of the lymphoepithelial cyst of the pancreas was established, as direct immunofluorescence could not be performed in formalin-fixed tissue, immunoperoxidase staining with C3d was obtained. C3 has a well-established

role in activation of complement and as a marker in BP. Deposition of C3d is a result of deactivation of C3b, a cleavage product of C3. In a study of 6 autoimmune blistering disorders that included 32 patients with BP, Pfaltz et al¹² found positive immunoperoxidase staining for C3d in 31 of 32 patients, which translated to a sensitivity of 97%, a positive predictive value of 100%, and a negative predictive value of 98% among the blistering diseases being studied. Similarly, Magro and Dyrsen¹³ had positive staining of C3d in 17 of 17 (100%) patients with BP.

In theory, any process that involves deposition of C3 should be positive for C3d on immunoperoxidase staining. Other dermatologic inflammatory conditions stain positively with C3d, such as systemic lupus erythematosus, discoid lupus erythematosus, subacute cutaneous lupus erythematosus, and dermatomyositis.¹³ The staining for these diseases correlates with the site of the associated inflammatory component seen on hematoxylin and eosin staining. The staining of C3d along the basement membrane of stratified squamous epithelium in the lymphoepithelial cyst of the pancreas seen in our patient closely resembles the staining seen in cutaneous BP.

A proposed mechanism for BP in our patient would be exposure of BP-1 antigen in the pancreatic cyst leading to antibody recognition and C3 deposition along the basement membrane in the cyst, as evidenced by C3d immunoperoxidase staining. The IgG and C3 deposition along the cutaneous basement membrane would then represent a systemic

response to the antigen exposure in the cyst. Thus, the lymphoepithelial cyst provided the immunologic stimulus for the development of the cutaneous BP. This theory is based on the observation of our patient's rapid improvement without a change in his treatment regimen immediately after surgical excision of the cyst.

Despite the plausibility of our hypothesis, several questions remain regarding the validity of our assumptions. Although sensitive for C3 deposition, C3d immunoperoxidase staining is not specific for BP. If the proposed mechanism for causation is true, one might have expected that a subepithelial cleft along the basement membrane of the pancreatic cyst would be observed, which was not seen. A repeat BP antigen antibody was not obtained, which would have been helpful in determining if there was clearance of the antibody that would have correlated with the clinical resolution of the BP lesions.

Conclusion

Our case suggests that paraneoplastic BP is a genuine entity. Indeed, the primary tumor itself may be the immunologic stimulus in the development of BP. Recalcitrant BP should raise the question of a neoplastic process that is exposing the BP antigen. If a thorough review of systems accompanied by corroborating laboratory studies suggests a neoplastic process, the suspect lesion should be further evaluated and surgically excised if clinically indicated. Further evaluation of neoplasms with advanced staining methods may aid in establishing the causative nature of tumors in the development of BP.

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