

# Bullous pemphigoid associated with nintedanib



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**Key words:** acneiform-like eruption; bullous pemphigoid; nintedanib; tyrosine kinase inhibitor.

## INTRODUCTION

Bullous pemphigoid (BP) is a subepidermal autoimmune blistering skin condition that is sometimes induced by numerous medicines.<sup>1</sup> We report the case of a patient who developed BP shortly after starting nintedanib, a tyrosine kinase inhibitor approved for treatment of idiopathic pulmonary fibrosis (IPF).

IPF is a progressive scarring disorder of the lung associated with significant mortality and morbidity. Although there is no cure for IPF, 2 medications appear to slow disease progression: nintedanib and pirfenidone.<sup>2</sup> Nintedanib works as a tyrosine kinase inhibitor, targeting numerous receptors, including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor.<sup>3</sup> The most common adverse effects from nintedanib are gastrointestinal events, mainly diarrhea.<sup>3,4</sup> Reports of adverse dermatologic effects from nintedanib are less common, and there are no reports, to our knowledge, of nintedanib-induced BP. Accordingly, the purpose of this case report is to shed light on BP as a possible adverse reaction to nintedanib.

## CASE REPORT

A 65-year-old man with IPF presented to the dermatology clinic with a pruritic, acneiform rash. He also reported a painful sore in his mouth. The patient first noticed the rash about 6 months prior, within weeks to a month after starting nintedanib for IPF. He was seen in urgent care and was prescribed 5% permethrin, which was not helpful, and triamcinolone 0.1% ointment, which offered some symptomatic improvement for the 1 week it

### Abbreviations used:

BP: bullous pemphigoid  
IPF: idiopathic pulmonary fibrosis

was recommended. At the time of the visit, he was taking 150 mg of nintedanib twice daily and had reached advanced stages of his disease, with plans for lung transplantation. He had been tolerating nintedanib, with mild nausea and gastrointestinal upset.

His other regular home medications were omeprazole and atorvastatin. When his symptoms began, he had been taking omeprazole for approximately 2 and a half years, and he had been taking atorvastatin for approximately 1 year (although it had been increased about 2 months before his presentation to our dermatology department). His medical history includes IPF, gastroesophageal reflux disease, coronary artery disease, herpes simplex virus, and former tobacco use.

Dermatologic examination was notable for a few intact vesicles and pustules on the forehead (Fig 1) and also numerous scattered 1- to 2-mm crusted papules with erythematous bases on the forehead, scalp, face, upper chest, and bilaterally on the knees (Fig 2). The examination also detected an oral linear ulcer.

The initial clinical differential included an acneiform-like drug reaction such as that seen with other tyrosine kinase inhibitors.<sup>5</sup> In addition, dermatitis herpetiformis was considered, given the small, crusted erosions clustered on the knees.

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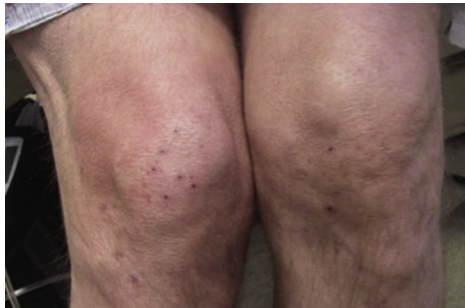
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**Fig 1.** Vesicle and multiple scattered papules with crust and erythematous bases on the left side of the patient's forehead. The purple dotted circles represent where punch biopsies were taken for H&E (left) and direct immunofluorescence (right).



**Fig 2.** Scattered 1- to 2-mm papules with crust and erythematous bases on the bilateral knees.

Two punch biopsies were performed on the left side of the forehead, 1 of a vesicle for H&E staining and the other of perilesional skin for direct immunofluorescence.

On histopathologic examination, there was a subepidermal vesicle formation with associated mixed neutrophilic and eosinophilic inflammation (Fig 3, A). Direct immunofluorescence studies showed linear immunoreactivity with IgG and C3 along the basement membrane (Fig 3, B). Laboratory studies showed positive IgG basement membrane zone antibodies with epidermal localization on human salt-split skin by indirect immunofluorescence (titer, 1:2560) and increased IgG BP180 level by enzyme-linked immunosorbent assay (96 units with a negative range of <9 units). Features were consistent with the diagnosis of BP.<sup>6</sup>

The patient was started on oral doxycycline 100 mg twice daily and oral niacinamide 500 mg 3 times daily for the treatment of BP without additional topical medications. He noted improvement of his rash on this regimen after 1 week. He has since undergone bilateral orthotopic lung transplantation; nintedanib, doxycycline, and oral niacinamide were discontinued 3 weeks after presentation to our dermatology department, and the rash has not recurred.

## DISCUSSION

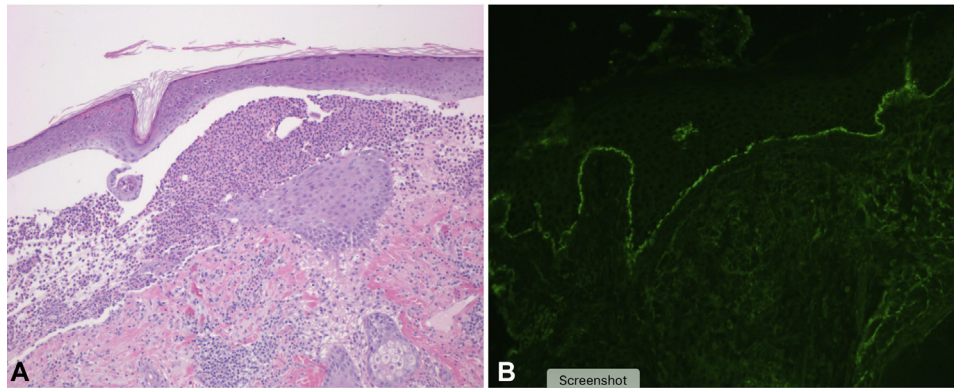
More than 50 drugs have been associated with the development of BP.<sup>1</sup> Here, we report an atypical case of BP that developed shortly after starting nintedanib.

The patient's histologic and immunofluorescence findings and positive BP180 antibodies are all consistent with BP.<sup>6</sup> However, his clinical presentation shared characteristics of the acneiform eruption seen in epidermal growth factor receptor–tyrosine kinase inhibitor adverse reactions. He also had an oral ulcer, which is uncommon in BP.<sup>7</sup> Notably, mucositis has been reported as the most common cutaneous serious skin reaction to nintedanib, although the linear palatal erosion would not be a common presentation for drug-induced mucositis.<sup>7,8</sup>

Although unsure of how nintedanib acted as a trigger for BP, we suspect that the blocking of multiple tyrosine kinase receptors (vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor) may somehow alter the antigenic properties of the epidermal basement membrane. Additional research is needed to define the role of tyrosine kinases in the pathogenesis of BP.

Although we cannot prove causation, we suspect that nintedanib induced BP in this case because of the temporal association between starting the drug and symptoms of BP. Furthermore, the patient's rash improved upon discontinuation of nintedanib. Unfortunately, this link between discontinuation of the medication and resolution of rash is complicated by the fact that he was started on lifelong immunosuppression after lung transplantation, which can also suppress skin findings. At the time of publication, he is using oral tacrolimus 1 mg twice daily, oral prednisone 40 mg once daily, and oral mycophenolate mofetil 1000 mg twice daily. Nonetheless, we find the temporal link convincing.

This unusual presentation of BP presented a diagnostic challenge and raises the importance of a broad differential when patients using tyrosine kinase inhibitors present with new skin findings. Recognition of BP as a possible adverse effect of nintedanib is important because withdrawal of the offending agent in drug-induced BP often leads to rapid resolution of symptoms without recurrence. This case also illustrates that BP may present in an atypical manner for patients started on nintedanib; the threshold for biopsy and further diagnostic studies should be low. Clinicians should be aware that BP may be an uncommon, but possible, adverse reaction to nintedanib.



**Fig 3.** **A**, A subepidermal split with inflammatory infiltrate composed of neutrophils and eosinophils. **B**, The direct immunofluorescence studies showed linear epidermal-dermal deposition of IgG.

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