

## Case Report

# Follicular lymphoma with paraneoplastic pemphigus as the first symptom: a case report and review of the literature

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**Abstract:** Paraneoplastic pemphigus (PNP) is an autoimmune bullous dermatosis associated with tumors, first described by Anhalt et al. in 1990. Reports of paraneoplastic pemphigus complicated by follicular lymphoma (FL) are rare in the medical literature. Here, we retrospectively analyze a case of PNP accompanied by FL. The patient was a 54-year-old woman who suffered from PNP associated with FL at the beginning. She had received a pathological diagnosis and was treated with R-CHOP and other drugs. Her mucosal lesions and cutaneous lesions improved, and the FL was in remission. Eleven months later, she died of BO after receiving the diagnosis of PNP. We also review most of the studies and reports about PNP accompanied by FL. We list the clinicopathologic features, therapeutic schedule, and prognosis in order to improve hematologists' understanding and treatment of the diseases.

**Keywords:** Follicular lymphoma, paraneoplastic pemphigus, bronchiolitis obliterans

## Introduction

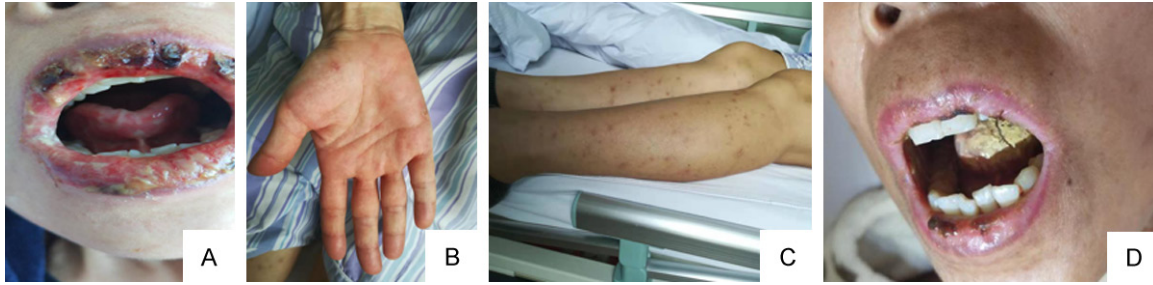
PNP is a rare paraneoplastic, systemic autoimmune bullous disease characterized by severe mucosal lesions and various cutaneous lesions. Most of the basic tumors originate from the lymphatic reticular system associated with Hodgkin's lymphoma, thymoma, and leukemia [1]. The patients suffering from PNP are characterized by autoantibodies acting against the plakin family of proteins. There are many patients with PNP who also get BO. An initial treatment with systemic corticosteroids is often attempted, and other immunosuppressive agents are also used in combination with systemic corticosteroids in patients who have PNP [2]. However, most patients have a poor prognosis independent of the status of the underlying neoplasms [3]. Though treatments for neoplasms are effective particularly in FL, in PNP associated with malignant neoplasms, the response of PNP to the treatment of the underlying neoplasm appears to be less favorable [4].

Bronchiolitis obliterans (BO) is a life-threatening form of irreversible, obstructive lung disease. Cases of BO were first reported in 1999, and BO may occur in chronic graft-versus-host disease patients undergoing allogeneic hematopoietic stem cell transplantation [5]. Evidence confirms that the BO can form after PNP, and it is a major cause of death in PNP patients.

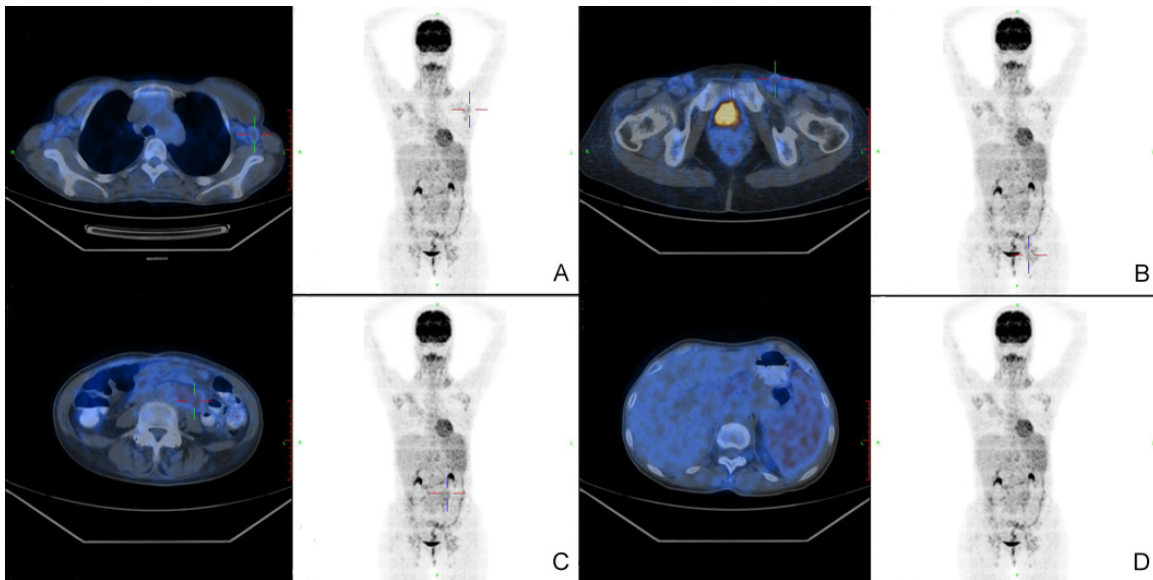
## Case report

A 54-year-old woman was admitted to the hospital in March 2018 with itchy erythema on her limbs and trunk. Her eyes, mouth, and labia also had painful erosions. A dermatological examination showed blisters and erosions on her lips, tongue, mucosa, and labia (**Figure 1A**). Her pharynx mucosa and eyes were swollen. A purplish-red rash could be seen on her hands, feet, and torso (**Figures 1B, 1C**). The pimples were target-shaped, well-defined and partially colorfast when pressed. Computed tomography showed multiple enlarged lymph nodes in the bilateral axillary, mediastinal, retroperito-

## A case of PNP associated with FL



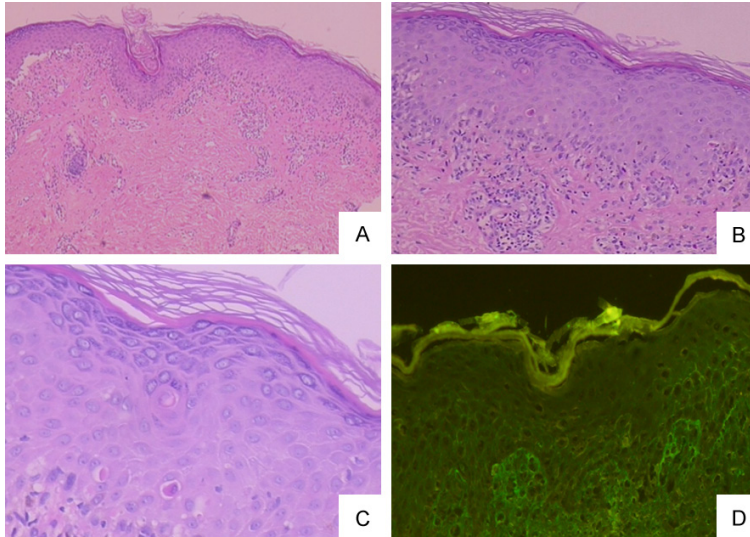
**Figure 1.** Blisters and erosion on the lips and erosion on the tongue mucosa (A). A purplish-red rash can be seen on her hands, feet, and torso (B, C). The pimples are target-shaped, well-defined, and partially colorfast when pressed. Oral mucositis and vulvar lesions improved during the treatment (D).



**Figure 2.** The PET-CT showed: enlarged lymph nodes in bilateral axilla (A), pelvic and bilateral inguinal (B), retroperitoneal (C); spleen enlargement (D).

neal and bilateral inguinal areas. Chronic inflammation was found in the lower lobe of both lungs. A PET-CT examination showed that: 1. FDG was increased in the tongue and right tonsil; 2. Enlarged lymph nodes were found in her bilateral neck region, bilateral supraclavicular region, bilateral pectoralis minor muscle, bilateral axilla (**Figure 2A**), mediastinum, abdominal cavity, mesentery, bilateral inguinal (**Figure 2B**), pelvis, and retroperitoneal space (**Figure 2C**); 3. Spleen enlargement (**Figure 2D**); 4. The FDG metabolism increased in all the above lesions. One week after admission, the patient underwent a thigh skin biopsy. Under a microscope, mild hyperkeratosis of the skin epidermis, an irregular thickening of the granular layer, edema, and a vacuole liquefaction of the basal

cells were observed. The small vessels in the superficial dermis were dilated around which the lymphocytes infiltrated densely and necrotic keratinocytes were seen in the epidermis (**Figure 3A-C**). Direct immunofluorescence (DIF) showed IgG deposition between the epidermal cells and the basement membrane zone (**Figure 3D**). One week after the skin biopsy, cervical and inguinal lymph node biopsies were performed: small atypical lymphocytes showed a nodular hyperplastic pattern in the lymph nodes. Those nodules were back to back, the nuclei were cleaved, and the chromatin was fine-grained (**Figure 4A**). Immunohistochemistry showed that the tumor cells were positive for CD20 (**Figure 4B**), CD10 (**Figure 4C**), Bcl-2 (**Figure 4D**), and Bcl-6 but negative for CD3, CD5,



**Figure 3.** Mild hyperkeratosis of the skin epidermis, irregular thickening of the granular layer, edema, and vacuole liquefaction of the basal cells. The small vessels in the superficial dermis dilated, lymphocytes infiltrated densely around the vessels, and necrotic keratinocytes were seen in the epidermis (A-C). Direct immunofluorescence (DIF) showed IgG deposition between the epidermal cells and the basement membrane zone (D).

and CyclinD1. Meshwork showed that the CD21 (Figure 4E) and CD23 were slightly irregular, and the positive rate of Ki67 (Figure 4F) was about 20%. Combined with the morphology and the immunohistochemical results, the lesions were consistent with grade I FL. A bone marrow biopsy showed the bone marrow was involved. A diagnosis of FL with PNP was made, and the patient was then transferred to the Department of Hematology for treatment with R-CHOP (rituximab, cyclophosphamide, epirubicin, vincristine, prednisone). During her standard course of chemotherapy, she received methylprednisolone tablets, recombinant human interleukin, and sodium thiosulfate. And she also improved with the administration of recombinant bovine basic fibroblast growth factor, erythromycin eye ointment, Tobradex ophthalmic ointment, and potassium permanganate sitz baths (1:10,000). The oral mucositis and vulvar lesions were relieved during the treatment (Figure 1D), but the patient died of a pulmonary infection and bronchiolitis obliterans eleven months after her diagnosis in February 2019.

### Discussion

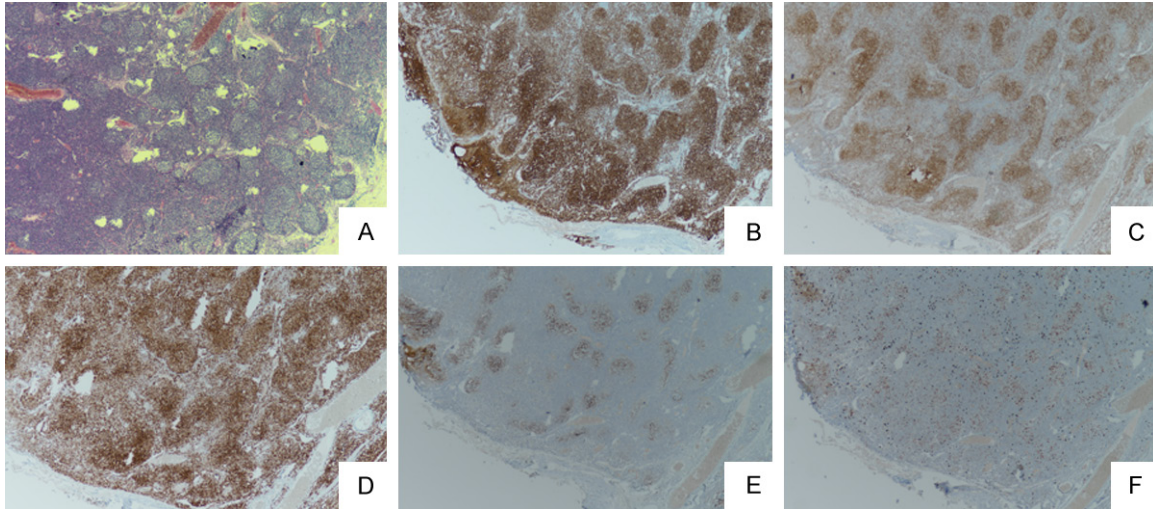
Reports of PNP associated with FL are relatively rare in the medical literature. There are 16 cases of patients who suffered from FL with

PNP reported in the English-language medical literature [6-21]. The clinical pathology characteristics can be drawn from these cases (Table 1): ① The patients' ages range from 49 to 77 years old with a median age of 61; ② Gender: there are 8 males and 9 females with a ratio of M:F=8:9; ③ 6/17 of the patients' clinical stages are IV; ④ 6/17 of the patients' FL classifications are grade I; ⑤ PNP occurrence time: most patients (10/17, 58.8%) also had occurrences of primary tumors; ⑥ During the course of the disease, 5/17 of the patients had secondary symptoms of BO within 1 week to 11 months after the appearance of PNP, and half of 8 patients died directly from BO induced by respiratory fail-

ure (4/8, 50%); ⑦ 16 of the 17 patients received chemotherapy with rituximab (16/17, 94.1%) and 8 patients were treated with an R-CHOP regimen (8/16, 50.0%). According to the literature, the maximum survival time of the 17 patients was 42 months, and the maximum survival time of the patients with BO was only 27 months.

PNP is a rare and lethal type of paraneoplastic autoimmune skin vesicular disease [1]. The diagnosis of paraneoplastic pemphigus depends on a histopathological examination and a direct or indirect immunofluorescence examination. The clinical features include painful mucosal erosions and pleomorphic skin lesions which can be involved in the skin and mucosa of the whole body, and the damage is severe and extensive. There are also large patches of purple erythema, blisters, moss-like, keratinizing lesions, and special serum immunoprecipitation. The histopathological characteristics include acantholysis, the formation of intraepithelial blisters, necrosis of the keratinocytes and an infiltration of inflammatory cells dominated by lymphocytes in the superficial dermis. IgG and C3 depositions between the epidermal cells and/or the basement membrane can be seen using a direct immunofluorescence (DIF) examination, and positive pemphigus antibod-

## A case of PNP associated with FL



**Figure 4.** Small atypical lymphocytes showed a nodular hyperplasia pattern in the lymph nodes. Those nodules were back to back, the nuclei were cleaved and the chromatin was fine-grained (A). Immunohistochemistry showed that the tumor cells were positive for CD20 (B), CD10 (C), and Bcl-2 (D). The meshwork seen using CD21 (E) was slightly irregular, and the positive rate of Ki67 (F) was about 20%.

ies based on mouse bladder epithelia is seen using indirect immunofluorescence (IIF) [22].

FL is a type of indolent B cell lymphoma derived from follicular central cells and central blasts. The mechanism of incorporating PNP is not yet clear, but PNP is closely related to the primary tumor. Published studies indicate that after the primary tumor is treated, the PNP symptoms improve. Takashi and others [12] believe that the use of bendamustine can trigger PNP because the skin toxicity of the drug causes a well-known adverse reaction. But the patient Jain et al. reported on [14] was treated with bendamustine/rituximab, and the PNP didn't appear until 29 months after the treatment. Therefore, the relationship between bendamustine and PNP needs to be explored further. Braess [23] believed that fludarabine seems to induce or worsen the process of PNP. But summarizing the prognosis of three patients treated with fludarabine, he indicated that the induction of fludarabine cannot be denied, for two of the patients did not achieve a longer survival time from this treatment plan. The immunological features of patients with PNP include the presence of autoantibody-recognizing proteins in the stratified squamous epithelium, the transitional columnar epithelium, and the monolayer epithelium in sera. So they were positive for DIF and IIF. Complement and immunoglobulin have been confirmed to have antitumor activity in a variety of tumors [24, 25]. Increased immu-

noglobulins and complements in cancer patients are self-protective responses. But most of the tumors that are associated with PNP originate from the lymphatic reticulum system, and whether they are related to the chemotherapeutic drugs or to the characteristics of the tumor itself needs further research.

The treatment for PNP mainly includes the treatment for the primary tumors, skin and mucosal damage, and for the complications of the affected organs [22]. The treatment of primary tumors is critical, and the involved skin and mucosa can be improved after treating the primary tumors [26]. R-CHOP is a first line chemotherapy regimen for FL and is effective for patients with PNP [21, 27]. The application of rituximab in this scheme can kill tumor cells and B cells. Based on the summary of the current relevant literature, FL patients with PNP treated with rituximab or R-CHOP can achieve tumor remission or even complete remission. But the rash and mucosal lesions cannot be completely cured. This phenomenon may be caused by the continuous release (or helpful release) of a specific antibody in the patient. For skin and mucosal lesions, we often chose a large dose of glucocorticoid and maintain it in small doses. Although this can alleviate skin and mucosal lesions to a certain extent, the patient's resistance is severely damaged. Regarding the above patients, most did not have a good survival time during the follow up period.

## A case of PNP associated with FL

**Table 1.** The main clinical features of the 17 FL patients with PNP or BO

Case Num.	References	Age	Gender	Clinical stage	FL Level	Diagnostic Time of PNP	Diagnostic Time of BO	Treatment Plan	Curative effect	Prognosis
1	Moustafa, et al. [6]	68	M	Unknown	I	Simultaneous diagnosis with tumor	Unknown	B*/R*→R*/Prednisone	Improvement of skin lesion Tumor shrinking The symptoms of infection are still repeated.	Died of infectious complications 10 months after diagnosis.
2	Lee, et al. [7]	53	M	IVA	Unknown	Simultaneous diagnosis with tumor	Simultaneous diagnosis with PNP	R-CHOP*	Complete remission of tumor, stomatitis, other skin lesions and BO are persistent existence.	Died of respiratory failure caused by BO 27 months after diagnosis.
3	Borradori, et al. [8]	61	F	Unknown	I	Simultaneous diagnosis with tumor	Unknown	P*→CHOP*/antibiotics/Cyclosporin/0.5% Retinaldehyde/Sucralfate→R*	The tumor was relieved and there was no progress. Stomatitis and palmar erythema were relieved and the patient was well tolerated by rituximab.	Unknown
4	Aoi, et al. [9]	60	M	Unknown	Unknown	Simultaneous diagnosis with tumor	Unknown	P*→P*/R*→R* combined with chemotherapy	The condition improved and the skin lesion recovered. The FL was relieved partly.	Unknown
5	Lim, et al. [10]	58	M	Unknown	Unknown	Simultaneous diagnosis with tumor	1 week after PNP diagnosis	Before BO: R-CHOP* AfterBO: R-CHOP*	Atypical pneumonia caused by cytomegalovirus infection one week after treatment.	Died of septic shock one month after diagnosis of BO.
6	Lachenal, et al. [11]	52	F	Unknown	Unknown	Simultaneous diagnosis with tumor	Unknown	R-CHOP*	The skin lesions were improved obviously, the oral erosion was improved, but the tumor reaction was unknown.	Unknown
7	Higo, et al. [12]	77	F	Unknown	Unknown	Simultaneous diagnosis with tumor	Unknown	R-CHOP*→Bendamustine/R*→Prednisone	The skin lesion recovered and the mucosal rash did not improve.	Unknown
8	Morikawa, et al. [13]	65	F	IIIA	Unknown	Simultaneous diagnosis with tumor	5 months after FL diagnosis	Before BO: R-CHOP*→R*→R-CVP* After BO: Palliative and symptomatic treatment	The tumor shrank and the symptoms such as conjunctivitis, oral mucosal ulcer and the rash improved.	Unknown
9	Jain, et al. [14]	60	M	IVB	I	29 months after FL diagnosis	Unknown	Bendamustine/R*→R*	The tumor was remission completely at the beginning and relapsed after 18 months.	Unknown
10	Hirano, et al. [15]	60	M	Unknown	Unknown	Simultaneous diagnosis with tumor	3 months after FL diagnosis	Before BO: R*/Prednisone After BO: Plasma exchange →R-CHOP*→Bendamustine/R*	The blisters disappeared completely and the autoantibodies decreased to the normal level. But the BO appeared later.	Died 7 months after the diagnosis of BO.
11	Hoque, et al. [16]	49	F	Unknown	Unknown	9 years after FL diagnosis	Unknown	CHOP*→Radiotherapy/F*/Mitoxantrone/Prednisone→F→R-CVP*	The tumor was completely relieved, the rash improved after treatment, but the general condition of the patient was poor.	After the occurrence of PNP, the condition worsened and the patient died after palliative treatment.
12	Martínez, et al. [17]	70	F	IVA	I	4 years after FL diagnosis	Unknown	CHOP*→Chlorambutyronitrile→P	The tumor was completely relieved, the skin blisters disappeared, but the lesions of oral mucosa persisted.	40 months after the diagnosis of PNP, there was no recurrence of skin and mucosal lesions.
13	Prodanovic, et al. [18]	73	M	IV	I	3 years after FL diagnosis	Unknown	R*/F*/D*/Mitoxantrone/Granisetron→R*	The tumor was relieved, the skin blisters were cured and there was no recurrence during the follow-up period.	Unknown

## A case of PNP associated with FL

14	Maruta, et al. [19]	70	M	IVB	Unknown	5 years after FL diagnosis	Unknown	Chlorambutyronitrile/ C*/O*→P*/F*/ Chlorambutyronitrile→P*/Rad iotherapy→Chlorambutyronitri le/P*→D*/Azathioprine→R*/P*	The tumor was relieved, the skin lesions were improved, but the oral mucosal lesions were relieved very little.	Died of left heart failure and pulmonary edema 9 months after the diagnosis of PNP.
15	Heizmann, et al. [20]	73	F	Unknown	Unknown	Simultaneous diagnosis with tumor	Unknown	P*/C*→R*/P*	The tumor was relieved partly and conjunctival and mucosal erosion recovered completely.	Unknown
16	Barnadas, et al. [21]	77	F	IIB	Unknown	Later than FL diagnosis time, the certain time is unknown	Unknown	Chlorophenylbutyronitrile→P*/ Valaciclovir→R*/P*→P*/Cyclo- sporin	The tumor was relieved partly and the oral ulcer was completely cured.	The patient died 42 months after the FL diagnosis. The cause of death is unknown, but acid-fast bacilli is active.
17	Present case	54	F	IV	I-II	Simultaneous diagnosis with tumor	11 months after FL diagnosis	R-CHOP* and so on	The FL was relieved and mucositis and vulvar lesions were improved.	Died of respiratory failure caused by BO 11 months after the diagnosis of PNP.

\*R: Rituximab; C: Cyclophosphamide; O/V: Vincristine; P: Prednisone; D: Dexamethasone; F: Fludarabine.

Regardless of whether BO appears, the patients often die from respiratory infections from which we can infer that the use of chemotherapeutics and glucocorticoids has a direct relationship between the suppression of the patients' auto-immune function and atelectasis.

About 30% of patients with PNP also suffer from BO, and the mechanism [28, 29] involves the infiltration of T cells below the bronchial tubes, as determined by autopsies. In addition, immunoglobulin and complement are deposited in the bronchial columnar epithelium, resulting in the exfoliation of the respiratory tract ciliated columnar epithelium from the basal cell layer. Mixed inflammatory infiltration composed of lymphocytes, neutrophils, eosinophils, and plasma cells can be seen in the submucosa. Nousari's experiment [28] confirmed that the acantholysis of the respiratory epithelium caused by Plakin proteins can lead to distal bronchial occlusion and scar formation, which gradually block the bronchioles. Then they cause breathing difficulties and aggravate respiratory infections. Therefore, we believe that the secondary BO symptoms in patients with PNP are irreversible pathological changes caused by the deposition of autoimmune antibodies associated with tumor tissues in the bronchiolar mucosa.

BO usually occurs quickly and irreversibly in the terminal stage of the disease, eventually leading to fatal respiratory failure. Patients with BO have a poor prognosis [30] and BO has become the leading cause of death in patients with PNP. Theoretically, patients can receive a lung transplant after the appearance of BO. But due to the lack of available lungs, the anti-host response after transplantation, and the chance that the BO will reappear after the transplantation, many clinical studies are needed to confirm this theory. Bronchoscopic transmural or open lung biopsies are often missed due to the lesions mainly involving the terminal or respiratory bronchioles and showing an uneven patchy or patch distribution. Therefore, clinical doctors often based their examinations on symptoms, pulmonary function, and imaging manifestations in order to reach a comprehensive diagnosis [31, 32].

For such patients who may have BO, pulmonary function measurement and fiberoptic bronchoscopy should be started earlier. They should

determine whether the patient has diffuse lung retention (in the expiration phase), bronchial thickening, or secondary dilatation using HRCT as soon as possible [32-35]. As for the absence of specific medicines, it is necessary to find out whether the patients have BO in time in order to strengthen the management of the respiratory tract and to inhale oxygen earlier, control the increase of inflammation, and improve their breathing difficulties.

### Summary

FL with PNP is rare. Grade 1 and clinical stage IV of FL are more common. The emergence of PNP indicates the potential of tumors and then the need to actively look for primary lesions. The mechanism of BO in PNP patients associated with FL is still unclear, and preventing the occurrence of BO is still a clinical challenge.

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### Disclosure of conflict of interest

None.

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## A case of PNP associated with FL

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## A case of PNP associated with FL

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