CASE REPORT

Cryptococcus neoformans empyema in a patient receiving ibrutinib for diffuse large B-cell lymphoma and a review of the literature

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SUMMARY

We report a case of *Cryptococcus neoformans* pulmonary infection complicated by empyema in a 79-year-old man with diffuse large B-cell lymphoma treated with R-CHOP and ibrutinib. A literature review identified 25 cases of cryptococcal pleural disease published since 1980. Most cases were caused by the *C. neoformans* species in immunocompromised hosts with an exudative pleural effusion and lymphocyte-predominant infiltrate. The cryptococcal antigen test was often positive when pleural fluid and serum were tested. The outcome was favourable in most cases with antifungal therapy and either thoracocentesis or surgical resection. We also identified 40 cases of opportunistic infections, most commonly aspergillosis, cryptococcosis and *Pneumocystis jirovecii* pneumonia, in patients treated with ibrutinib. *In vitro* studies indicate Bruton tyrosine kinase inhibition impairs phagocyte function and offer a mechanism for the apparent association between ibrutinib and invasive fungal infections.

BACKGROUND

Cryptococcus neoformans is an encapsulated yeast that causes infection in immunocompromised and, less commonly, immunocompetent patients. Pleural infection, either in isolation or secondary to pulmonary disease, is a rare manifestation of cryptococcosis. Although a report of two cases and a review of the literature published in 1980 identified 28 cases dating back to 1941,[1] the vast majority of these cases predate contemporary diagnostic methods of antigen testing and ribosomal DNA internal transcribed spacer sequencing (rDNA ITS). Ibrutinib is an irreversible Bruton tyrosine kinase (BTK) active site inhibitor approved for use in various B-cell haematological cancers since 2015, including chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL), small lymphocytic lymphoma and Waldenström macroglobulinaemia (WM). Although it was thought to selectively target B lymphocytes, there is a growing body of literature describing opportunistic infections typically associated with decreased phagocyte number and function in patients receiving ibrutinib therapy. We describe a case of pulmonary *C. neoformans* infection complicated by empyema in a patient receiving ibrutinib for diffuse large B-cell lymphoma (DLBCL) and review the literature of pleural cryptococcal disease and ibrutinib-associated opportunistic infections.

CASE PRESENTATION

A 79-year-old man presented in May 2017 with progressive left-sided pleuritic chest pain and dyspnoea for 1 week. His medical history included DLBCL stage IV diagnosed 2 months earlier with nodal disease within the neck, chest, abdomen and pelvis, and extranodal disease of the base of skull, bone marrow, ribs and thigh muscles. The patient had commenced R-miniCHOP with rituximab 375 mg/m^2, cyclophosphamide 400 mg/m^2, doxorubicin 25 mg/m^2 and vincristine 1 mg intravenously on day 1 and prednisolone 40 mg/m^2 on days 1–5 of the 21-day cycle 6 weeks earlier. The patient presented at cycle 2 day 21 and had been scheduled to commence cycle 3 the following day. The patient was enrolled in the ALLG NHL29 trial through which he had also received ibrutinib 560 mg orally daily for the preceding 6 weeks. He was diagnosed with latent *Mycobacterium tuberculosis* infection via a positive screening interferon-γ release assay and commenced isoniazid 300 mg orally daily at the same time as chemotherapy. The patient was a gardener and he denied wearing a mask while handling chicken manure and soil. On examination, the patient exhibited hypoxaemia with a SpO_2 of 93% on room air, tachypnoea with a respiratory rate of 22 breaths per minute, and low-grade fevers. The heart rate and blood pressure were within normal ranges. Breath sounds were decreased over the left lower zone.

INVESTIGATIONS

Blood test results demonstrated a leucocytosis (11.4×10^9/L) with neutrophilia (7.4×10^9/L), normal lymphocyte count (2.7×10^9/L), mild anaemia (114 g/L), mild thrombocytopenia (132×10^9/L), and elevated serum C reactive protein (58 mg/L) and D-dimer (0.89 mg/L) levels. Serum electrolyte, urea, creatinine, bilirubin, liver enzyme, creatine kinase, and troponin levels were within the reference ranges. The serum immunoglobulin levels were not measured at the time of presentation but were normal 2 months earlier. Peripheral blood lymphocyte subsets were not performed. An X-ray chest demonstrated a small left pleural effusion and associated collapse/consolidation. Nasopharynx and throat respiratory pathogen multiplex PCR (AusDiagnostics) and urine Legionella and Pneumococcus antigen tests (Binax) were negative. A CT pulmonary angiogram demonstrated multiple

parenchymal and subpleural nodules bilaterally measuring up to 14 mm in diameter, ground-glass opacification of the inferior lingular segment, a small left pleural effusion, and subsegmental atelectasis of the left and right lower lobes. The lymphadenopathy in the chest demonstrated on the staging CT and PET–CT had resolved. The patient commenced azithromycin 500 mg intravenously daily and ceftriaxone 1 g intravenously daily. An induced sputum specimen was obtained. No fungal elements were observed with acridine orange staining and microscopy but fungal cultures demonstrated growth of *Candida albicans*, thought to represent upper airway colonisation. Acid-fast bacilli microscopy and culture (6 weeks' incubation) and *M. tuberculosis* and *Pneumocystis jirovecii* PCR testing were negative. Induced sputum cytology was not performed. Percutaneous biopsy of the largest pulmonary nodule in the left upper lobe was attempted, but the left pleural effusion had increased in size, obscuring the target. Instead, thoracocentesis of approximately 500 mL of blood-stained, turbid pleural fluid was performed. Pleural fluid biochemical testing demonstrated an exudate with lactate dehydrogenase and protein levels of 225 IU/L and 42 g/L, respectively. Polymorphonuclear cells were observed but an accurate cell count could not be performed as the specimen was grossly blood-stained. Pleural fluid cytology with H&E staining demonstrated a blood-stained smear with numerous eosinophils and neutrophils mixed with histiocytes, lymphocytes, and mesothelial cells without granulomas or malignant cells. Yeast cells were not detected on pleural fluid cytology. Flow cytometry demonstrated lymphocytes accounted for 15% of the cells (B cells: <1%; T cells: 96%) with no abnormal lymphocyte population. Acid-fast bacilli microscopy and culture (6 weeks' incubation) and *M. tuberculosis* and *P. jirovecii* PCR testing were negative. Acridine orange and Gram staining and microscopy demonstrated no fungal elements or bacteria and routine bacterial culture demonstrated no growth. The serum cryptococcal antigen test was positive at a titre of 1:40. The cryptococcal antigen test was also performed on undiluted pleural fluid and demonstrated a positive result. Blood cultures were not performed. A CT brain and paranasal sinus demonstrated no abnormalities. Lumbar puncture and cerebrospinal fluid (CSF) biochemical testing and microscopy were consistent with a traumatic tap while the CSF cryptococcal antigen test and CSF cultures were negative. Seven days after thoracocentesis was performed, the pleural fluid fungal culture was positive for *C. neoformans* identified via absence of growth on L-canavanine–glycine–bromothymol blue agar, VITEK2 and rDNA ITS.

TREATMENT

Antibiotic therapy was ceased and the patient commenced liposomal amphotericin B 300 mg (4 mg/kg) intravenously daily and flucytosine 2000 mg (25 mg/kg) orally daily but, due to acute kidney injury, was changed 4 days later to fluconazole 400 mg orally daily for 12 months.

OUTCOME AND FOLLOW-UP

The patient was readmitted with a pulmonary embolism 3 weeks later. A CT chest performed 2 months after commencing antifungal therapy demonstrated resolution of the pulmonary nodules. The patient's chemotherapy was suspended for 1 month following the diagnosis of cryptococcosis. He completed cycles 3–6 of R-miniCHOP chemotherapy with ibrutinib and then cycle 7 of methotrexate and rituximab and cycle 8 of rituximab alone due to possible methotrexate-induced pulmonary fibrosis in September 2017. Complete remission of his DLBCL was achieved on bone marrow biopsy and PET–CT in November 2017. In April and May 2018, the patient developed left shoulder pain and serial CT chests demonstrated a slowly enlarging left hilar soft-tissue mass without lymphadenopathy, which is currently undergoing further investigation.

DISCUSSION

We conducted a literature review of Embase, Medline, PubMed and Scopus and identified 25 cases of cryptococcal pleural infections described in 23 publications in English since 1980. These cases are summarised in table 1. Infection was disseminated in 11 cases, including central nervous system infection in 10 cases, fungaemia in four cases, cutaneous infection in two cases, and peritoneal infection in one case, and localised to the lung parenchyma and pleura in 14 cases, including two cases with pleural masses without parenchymal lung disease. *C. neoformans* accounted for 22 of the cases and *C. laurentii* accounted for one case while the species was not reported in two cases. Immunocompromise was present in 20 of the 25 cases, with the most common causes including HIV infection (seven cases), solid organ transplantation (five cases), and cancer (four cases). The serum cryptococcal antigen test was positive in 15 cases with a median titre of 1:256 (range, 1:32–1:4096), negative in three cases and not performed in seven cases. Twenty-three cases underwent thoracocentesis while surgical resection was performed in the two cases with pleural masses. The pleural fluid cryptococcal antigen test was positive in all 11 cases in which it was performed, with a median titre of 1:256 (range, 1:18–1:8192). Pleural fluid fungal staining and microscopy was positive in four cases and negative in 19 cases while pleural fluid culture was positive in 17 cases and negative in six cases. The pleural fluid biochemistry demonstrated an exudate in 16 cases, a transudate in one case, and was not reported in six cases. Cytology demonstrated lymphocyte predominance in nine cases, neutrophil predominance in four cases, and monocyte predominance in one case, and was not reported in nine cases. Cytological examination did not identify yeast in any of the case reports. The pleural fluid adenosine deaminase level was reported in four cases and elevated in two cases, both of which were initially treated with antituberculosis antibiotics. Amphotericin B (conventional or liposomal) was administered as induction therapy in 19 cases and in combination with flucytosine in nine cases. Azoles were administered as induction therapy in five cases and in combination with flucytosine in one case. The duration of antifungal therapy ranged from 3 weeks to 12 months but was not reported in many of the cases, most likely because antifungal therapy was ongoing at the time of publication. The outcomes were favourable, with only 2 of the 25 patients dying, one from cryptococcosis and one from metastatic squamous cell carcinoma 6 weeks later. The outcome was not reported in one case.

Ibrutinib, an irreversible BTK inhibitor that decreases B lymphocyte function, proliferation and survival, has proven an effective treatment for B lymphocyte haematological cancers. Complement cascade, phagocyte, and T lymphocyte defects have been described in patients with B lymphocyte CLL.[2] However, a growing body of literature documents opportunistic infections not typically associated with B lymphocyte dysfunction in patients receiving ibrutinib therapy and suggests a causal link to this medication. A literature review was performed, identifying 40 cases of opportunistic infections in patients receiving ibrutinib therapy. These cases are summarised in table 2. The patient described in our case report was older, aged 79 years,

Table 1 Cryptococcal pleural disease case reports

Reference	Age/sex	Disease	*Cryptococcus* species	Comorbidities	Pulmonary lesion(s)	Microbiological diagnosis				Treatment	Outcome
						Blood	CSF	Pleural fluid	Other		
Gera *et al*[16]	59/F	Localised	NR	Rheumatological disease not specified (prednisolone (dose NR))	Consolidation (right upper lobe) Pleural mass (right)	Ag test + (titre NR)	NA	NA	Pleura: biopsy and histopathology + (HE)	Fluconazole (duration NR)	Recovered
Chen *et al*[17]	63/M	Disseminated (CNS disease+fungaemia)	*C. neoformans*	Renal transplantation (mycophenolate mofetil, prednisolone (dose NR), tacrolimus for 17 months)	Nodules (bilateral) Pleural effusion (left)	Ag test + (1:1280) Culture +	Culture +Microscopy + (India ink)	Exudate Lymphocyte-predominant ADA (121 IU/L) Culture – Microscopy –	Pleura: biopsy and histopathology – initially, + on review (H&E, MS, PAS)	Amphotericin B+flucytosine+voriconazole for 11 days then amphotericin B+flucytosine for 8 weeks then fluconazole	Recovered
Yoshino *et al*[18]	51/M	Localised	*C. neoformans*	HBV infection (chronic) HIV infection (new diagnosis, $CD4^+$ T-cell count 49/µL)	Pleural effusion (left)	Ag test + (titre NR)	Ag test – Culture – Microscopy – (India ink stain)	Exudate Cell predominance NR ADA (85.9 IU/L) Culture + Microscopy –	Sputum: culture –	Amphotericin B for 2 weeks then fluconazole for 8 weeks ART 6 weeks after antifungal therapy initiation	Recovered
Kinjo *et al*[19]	64/M	Localised	*C. neoformans*	End-stage kidney disease+HD HTLV-1 infection	Pleural effusion (right)	Ag test –	Ag test – Culture –	Exudate Lymphocyte-predominant ADA (33.2 IU/L) Ag test + (titre NR) Culture + Microscopy –	Pleura: biopsy and histopathology – (GMS)	Amphotericin B+flucytosine for 9 days then fluconazole for 6 months	Recovered
Izumikawa *et al*[20]	24/M	Localised	*C. neoformans*	None	Consolidation (right lower lobe) Pleural effusion (right)	Ag test + (1:1024)	Ag test – Culture – Microscopy – (India ink stain)	Exudate Cell predominance NR Ag test + (1:256) Culture – Microscopy – PCR +	BAL: Ag test + (1:64) BAL: microscopy + (India ink stain) Pleura: biopsy and histopathology + (GMS, PAS) Sputum: culture –	Itraconazole for 13 days (fever recurrence and pleural effusion increasing) then amphotericin B for 7 days then flucytosine+voriconazole for 6 months	Recovered
Kamiya *et al*[21]	83/M	Disseminated (abdominal+CNS disease+fungaemia)	*C. neoformans*	Cryptogenic organising pneumonia (prednisolone daily (dose NR)) Myelodysplastic syndrome	Consolidation and ground glass opacification (right lower lobe) Pleural effusion (right then bilateral)	Ag test + (1:4096) Culture +	Ag test + (1:256) Culture –	Exudate (L+R) Cell predominance NR Ag test + (L: 1:256, R: 1:4096) Culture – Microscopy + (GS)	Ascitic fluid: Ag test + (1:512) Ascitic fluid: culture – Lung: biopsy and histopathology + (H&E)	Amphotericin B for 4 weeks (renal dysfunction) then fluconazole for 15 days	Died
Shankar *et al*[22]	35/F	Localised	*C. laurentii*	Diabetes mellitus HIV infection ($CD4^+$ T-cell count 17/µL) Tuberculosis	Pleural effusion (left)	NA	NA	Biochemistry NR Cell predominance NR Culture + Microscopy –	Sputum: culture +	Fluconazole for 5 weeks	Recovered
Chang *et al*[23]	22/M	Localised	*C. neoformans*	None	Rib mass (left ninth) Pleural effusion (loculated, left)	Ag test + (1:256)	NA	Exudate Neutrophil-predominant Culture + Microscopy –	Rib: resection and histopathology +	Thoracotomy and decortications and rib resection and amphotericin B single dose then fluconazole for 30 days	Recovered
de Klerk *et al*[24]	18/F	Disseminated (CNS disease)	NR	None	Pleural mass (right)	NA	Ag test + (titre NR)	NA	Pleural mass: biopsy and histopathology + (H&E)	Amphotericin B for 3 weeks then pleural mass resection then NR	Recovered
Ramanathan *et al*[25]	49/M	Localised	*C. neoformans*	Diabetes mellitus Renal-pancreas transplantation (mycophenolate mofetil, prednisolone (dose NR), tacrolimus for 21 months)	Hilar lymph node (calcified, right) Pleural effusion (left)	Ag test + (1:32)	Ag test – Culture –	Exudate Lymphocyte-predominant Culture – Microscopy –	BAL: microscopy – (GMS) Pleura: biopsy and histopathology + (GMS, PAS) Pleura: biopsy and culture +	Fluconazole+flucytosine for 3 months then fluconazole for 2 months	Recovered

Continued

Table 1 Continued

Reference	Age/sex	Disease	*Cryptococcus* species	Comorbidities	Pulmonary lesion(s)	Microbiological diagnosis				Treatment	Outcome
						Blood	CSF	Pleural fluid	Other		
Wong *et al*[26]	30/F	Disseminated (CNS disease)	*C. neoformans*	None	Pleural effusion (bilateral)	Culture –	Ag test + (1:256) Culture +	Transudate Neutrophil-predominant Ag test + (titre NR) Culture – Microscopy –	Other	Amphotericin B and flucytosine for 11 weeks then fluconazole (duration NR)	Recovered
Fukuchi *et al*[27]	52/F	Localised	*C. neoformans*	Amyloidosis (new diagnosis, intestinal) End-stage kidney disease+HD Rheumatoid arthritis (prednisolone 10 mg daily)	Pleural effusion (left)	Ag test + (titre NR)	NA	Exudate Lymphocyte-predominant ADA (27.8 IU/L) Ag test + (1:64) Culture + Microscopy –	NA	Amphotericin B intravenous for 32 days and intraperitoneal for 28 days then flucytosine and fluconazole (duration NR)	Recovered
Mulanovich *et al*[28]	28/M	Localised	*C. neoformans*	HIV infection (new diagnosis, $CD4^+$ T-cell count 43/µL)	Consolidation (right lower lobe) Pleural effusion (right)	Ag test + (1:256) Culture –	NA	Exudate Neutrophil-predominant Ag test + (1:64) Culture + Microscopy –	NA	Amphotericin B+flucytosine for 8 days (ceased due to leucopenia) then fluconazole for 12 months	Recovered
de Lalla *et al*[29]	26/M	Disseminated (CNS disease)	*C. neoformans*	HIV infection (new diagnosis, $CD4^+$ T-cell count 200/µL)	Pleural effusion (left)	Ag test + (1:256) Culture –	Ag test + (1:4) Culture +	Exudate Cell predominance NR Ag test + (1:8192) Culture + Microscopy –	NA	Amphotericin B+flucytosine for 10 days then amphotericin B for 5 days then fluconazole for >6 months	Recovered
Lye *et al*[30]	59/F	Disseminated (CNS and cutaneous disease and fungaemia)	*C. neoformans*	Renal transplantation (azathioprine 5 mg daily, cyclosporine 4 mg/kg daily, OKT3, prednisolone 10 mg daily)	Pleural effusion (right)	Ag test + (1:256) Culture +	Ag test + (1:256) Culture +	Exudate Cell predominance NR Culture – Microscopy –	Pleura: biopsy and histopathology + Skin: biopsy and histopathology + Sputum: culture –	Fluconazole for 6 months	Recovered
Taguchi *et al*[31]	70/F	Localised	*C. neoformans*	HTLV-1 infection (new diagnosis) Waldenström macroglobulinaemia (new diagnosis)	Pleural effusion (bilateral)	Ag test – Culture –	NA	Biochemistry NR Cell predominance NR Ag test + (1:16) Culture + Microscopy –	NA	Miconazole intravenous and intraperitoneal for 3 weeks	Recovered
Tenholder *et al*[32]	46/M	Localised	*C. neoformans*	Laryngeal cancer and laryngectomy and neck lymph node dissection and radiotherapy (12 months previously)	Nodules (bilateral) Pleural effusion (right, loculated)	NA	NA	Biochemistry NR Cell predominance NR Culture + Microscopy + (H&E)	Bronchial brushings: culture + Bronchial brushings: Microscopy + Lung: biopsy and culture + Lung: biopsy and histopathology + (H&E)	Amphotericin B (duration NR) then amphotericin B+flucytosine (duration NR) then ketoconazole for 6 weeks	Died (6 weeks later from cancer)
Grum *et al*[33]	35/M	Disseminated (CNS disease)	*C. neoformans*	HIV infection ($CD4^+$ T-cell count NR) Substance dependence disorder+IVDU	Pleural effusion (right)	Ag test + (1:128)	Ag test + (1:256) Culture + Microscopy + (India ink stain)	Exudate Neutrophil-predominant Culture + Microscopy –	NA	Amphotericin B (duration NR)	Recovered

Continued

Table 1 Continued

Reference	Age/sex	Disease	*Cryptococcus* species	Comorbidities	Pulmonary lesion(s)	Microbiological diagnosis				Treatment	Outcome
						Blood	CSF	Pleural fluid	Other		
Conces *et al*[34]	22/M	Localised	*C. neoformans*	CMV hepatitis (acute) Polycystic kidney disease Renal transplantation (azathioprine, prednisolone (dose NR))	Consolidation (left lower lobe) Pleural effusion (left)	NA	Ag test – Culture –	Biochemistry NR Monocyte-predominant Culture + Microscopy –	NA	Amphotericin B+flucytosine (duration NR)	Recovered
	53/F	Disseminated (cutaneous disease)	*C. neoformans*	Polycystic kidney disease Renal transplantation (azathioprine, prednisolone (dose NR))	Pleural effusion (right)	NA	Ag test – Culture –	Biochemistry NR Cell predominance NR Ag test + (1:160) Culture + Microscopy + (stain NR)	Skin: biopsy and culture +	Amphotericin B (duration NR)	Recovered
Katz *et al*[35]	29/M	Disseminated (CNS disease and fungaemia)	*C. neoformans*	HIV infection (new diagnosis, $CD4^+$T-cell count NR)	Pleural effusion (right)	Ag test + (1:1024) Culture +	Culture +	Exudate Lymphocyte-predominant Culture + Microscopy –	Pleura: biopsy and histopathology +	Amphotericin B for 8 weeks	Recovered
Newman *et al*[36]	37/M	Disseminated (CNS disease)	*C. neoformans*	HIV infection (new diagnosis, $CD4^+$ T-cell count NR) Substance abuse disorder+IVDU	Pleural effusion (left)	Ag test + (1:128) Culture –	Ag test + (1:16) Culture –	Exudate Lymphocyte-predominant Culture + Microscopy –	BAL: Ag test – BAL: culture – BAL: microscopy – (GS, GMS, mucicarmine stain) Pleura: biopsy and histopathology – Sputum: culture –	Amphotericin B (duration NR)	Recovered
Winkler *et al*[37]	66/M	Localised	*C. neoformans*	Melanoma (metastatic)	Pleural effusion	NA	NA	Biochemistry NR Lymphocyte-predominant Culture + Microscopy + (Wright-Giemsa stain)	NA	NR	NR
Young *et al*[1]	42/M	Localised	*C. neoformans*	Chronic kidney disease Diabetes mellitus	Diffuse interstitial infiltrates Pleural effusion (right)	Ag test –	Ag test – Culture –	Exudate Lymphocyte-predominant Ag test + (1:4096) Culture + Microscopy –	NA	Amphotericin B+flucytosine (duration NR)	Recovered
	66/F	Disseminated (CNS disease)	*C. neoformans*	Acute kidney injury+PD+HD (new diagnosis) Hypertension Ischaemic heart disease	Pleural effusion (bilateral)	Ag test + (1:2048)	Ag test + (1:8) Culture +	Exudate Lymphocyte-predominant Ag test + (1:2048) Culture + Microscopy –	NA	Amphotericin B (duration NR)	Recovered

ADA, adenosine deaminase; ART, antiretroviral therapy; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; GMS, Grocott's methenamine silver; GS, Giemsa stain; HBV, hepatitis B virus; HD, haemodialysis; HTLV-1, human T lymphocyte virus-1; IVDU, intravenous drug use; NA, not applicable; NR, not reported; PAS, periodic acid–Schiff; PD, peritoneal dialysis.

Table 2 Opportunistic infections in patients receiving ibrutinib

Pathogen	Site	Age/sex	Cancer	Time since commencing ibrutinib (months)	Concurrent treatment/previous treatments	Hypogammaglobulinaemia/ lymphopenia/neutropenia	Treatment	Outcome	Reference
Aspergillus fumigatus	Lung	62/M	CLL	1.5	None/fludarabine+ rituximab (timing NR)	NR/absent (CD4 T-cell count: NR)/ absent	Voriconazole (duration NR)	Died (5 months later due to CLL)	38
Aspergillus nidulans	Cavernous sinus Orbit Sphenoid bone Sphenoid sinus	75/F	CLL	0.82	Rituximab/R FC × 6 cycles (December 2012–May 2013)	Absent/absent (CD4 T-cell count: NR)/absent	Voriconazole (duration NR)	Survived	39
Aspergillus spp	CNS Lung	76/NR	CLL	2.1	Rituximab/2 other therapies not specified	NR	NR	Died	40
Aspergillus spp	Lung	NR	CLL	NR	NR	NR	NR	NR	41
Aspergillus spp	Lung	65/F	CLL+DLBCL (EBV+)	1	None/R ESHAP then R-EPOCH (September 2013–March 2014)	NR/NR/absent	Voriconazole (duration NR)	Survived	42
Aspergillus spp	CNS (brain abscess)	NR	CLL	1	Glucocorticoids/NR	NR	NR	Died	43
Aspergillus spp	CNS (brain abscess)	NR	CLL	2	Glucocorticoids/NR	NR	LAMB (duration NR) then voriconazole for 12 months	Survived	43
Aspergillus spp	CNS (brain abscess)	NR	CLL	2	Glucocorticoids/NR	NR	LAMB (duration NR)	Survived	43
Aspergillus spp	CNS Lung	76/F	PCNSL	0.5	Glucocorticoids/none	NR	NR	Died	5
Aspergillus spp	CNS Lung	65/M	PCNSL	0.5	Glucocorticoids/none	NR	NR	Died	5
Aspergillus spp	CNS Lung	87/F	PCNSL	3	None/none	NR	NR	Died (due to PCNSL)	5
Aspergillus spp	CNS Lung	49/M	PCNSL	0.5	Glucocorticoids/none	NR	NR	Survived	5
Aspergillus spp	Lung	60/M	PCNSL	4	Glucocorticoids/none	NR	NR	Survived	5
Aspergillus spp	Lung	53/M	PCNSL	2	None/none	NR	NR	Survived	5
Aspergillus spp	Lung	64/M	PCNSL	1	Glucocorticoids/none	NR	NR	Survived	5
Aspergillus spp	NR	NR	WM	NR	None/rituximab, other therapies not specified	NR	NR	NR	44
Aspergillus spp	Lung	NR	PCNSL	NR	NR/other therapies not specified	NR	NR	Survived	45
Aspergillus spp	CNS	NR	PCNSL	NR	NR/other therapies not specified	NR	NR	NR	46
Aspergillus spp Mucormycosis	Lung	67/M	CLL	7	None/R-F (2011)	Present/absent (CD4 T-cell count: NR)/present	Voriconazole (duration NR)	Died	47
Cryptococcus neoformans	Blood Lung	68/F	CLL	1	None/chlorambucil+prednisolone×6 cycles (2012–2014)	Present/absent (CD4 T-cell count: NR)/absent	LAMB+flucytosine (2 weeks) then fluconazole (duration NR)	Survived	48
Cryptococcus spp	Blood Skin (diffuse purpuric rash)	71/M	MCL	4	Bortezomib (1 month previously)/R bendamustine×3 cycles (5–7 months previously), ibrutinib (1–5 months previously)	NR/NR/NR	Fluconazole then LAMB+flucytosine (duration NR)	Died	49
Cryptococcus neoformans	CNS (meningo-encephalitis) Skin (leg abscess)	74/F	WM	2	None/bortezomib+R-CHOP, R-FC, R-CD (2005–August 2014) then idelalisib (September 2014–March 2015)	Present/NR/absent	LAMB (duration NR)	Died	39
Cryptococcus neoformans	Blood CNS (meningitis) Lung	54/M	CLL	1	None/R FC (2014–2015)	NR/absent (CD4 T-cell count: NR)/ absent	LAMB+flucytosine for 2 weeks then LAMB+fluconazole for 2 weeks	Died	50
Cryptococcus neoformans	CNS (meningitis) Lung	88/M	WM	0.75	None/rituximab (2008), R-bendamustine (2012)	NR/present/absent	LAMB+flucytosine for 2 weeks then fluconazole lifelong	Survived	50
Cryptococcus spp	NR	NR	MCL	NR	NR	NR	NR	NR	51
Cryptococcus spp	Lung	NR	CLL	NR	NR	NR	NR	NR	52

Continued

Table 2 Continued

Pathogen	Site	Age/sex	Cancer	Time since commencing ibrutinib (months)	Concurrent treatment/previous treatments	Hypogammaglobulinaemia/ lymphopenia/neutropenia	Treatment	Outcome	Reference
Fusarium solani	Disseminated (skin lesions)	56/M	CLL	1.5	None/FMD×6 cycles (2007), R-CHOP×6 cycles then ibritumomab tiuxetan (2010), obinutuzumab+bendamustine×6 cycles (2014)	Present/absent (CD4 T-cell count: NR)/present	Voriconazole for 6 weeks then prophylaxis	Survived	53
Histoplasma capsulatum	NR	NR	MCL	NR	NR	NR	NR	NR	51
JC virus	CNS (progressive multifocal leukoencephalopathy)	65/M	CLL	1.75 (ibrutinib ceased 1 month prior due to pneumonia)	None/FC×5 cycles (2008), R-bendamustine×2 cycles (2012), cyclophosphamide+epirubicin+prednisolone×6 cycles (2013)	Present/NR/NR	Mefloquine+mirtazapine for 7 weeks	Died (7 weeks later from presumed aspiration pneumonia)	54
Mycobacterium tuberculosis	CNS (brain abscesses) Lung (miliary) Spine	64/M	CLL	1	None/7 other therapies including allogeneic haematopoietic stem cell transplantation	NR/absent (CD4 T-cell count: normal)/absent	Rifampicin, isoniazid, ethambutol and pyrazinamide (duration NR)	Survived	55
Pneumocystis jirovecii	NR	NR	MCL	NR	NR	NR	NR	NR	51
Pneumocystis jirovecii	Lung	69/M	CLL	1.9	None/none	NR/absent (CD4 T-cell count: NR)/ absent	Trimethoprim+sulfamethoxazole for 21 days then prophylaxis	Survived	56
Pneumocystis jirovecii	Lung	68/M	CLL	23.6	Glucocorticoids/none	Absent (IVIg replacement)/absent (CD4 T-cell count: 551/µL)/absent	Trimethoprim+sulfamethoxazole then atovaquone for 21 days then no prophylaxis	Survived	56
Pneumocystis jirovecii	Lung	72/M	CLL	1.9	None/none	NR/absent (CD4 T-cell count: NR)/ absent	Trimethoprim+sulfamethoxazole for 21 days then no prophylaxis	Survived	56
Pneumocystis jirovecii	Lung	78/M	CLL	6	None/other therapies not specified	Absent/absent (CD4 T-cell count: 966/µL)/absent	Trimethoprim+sulfamethoxazole for 14 days then no prophylaxis	Survived	56
Pneumocystis jirovecii	Lung	70/M	CLL	11.6	None/none	Absent/absent (CD4 T-cell count: 734/µL)/absent	Trimethoprim+sulfamethoxazole for 21 days then no prophylaxis (then prophylaxis 12 months later)	Survived	56
Pneumocystis jirovecii	Lung	NR	CLL	NR	None/other therapies not specified	NR	NR	NR	57
'Recurrent fungal pneumonia'	Lung	64/NR	CLL	20	None/3 other therapies not specified	NR	NR	Died	40
Mucor spp	Sinus	79/M	CLL	20	None/NR	Present (IgG level: 2.07 g/L)/present (total lymphocyte count: 320 cells/ µL)/present (neutrophil count: 520 cells/µL)	Isavuconazole+LAMB for 7 days then isavuconazole (duration NR)	Survived	58
Zygomycete	Skin	NR	CLL	NR	None/NR	NR	LAMB (duration NR) then posaconazole (duration NR)	Died (due to CLL)	59

CLL, chronic lymphocytic leukaemia; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; FMD, fludarabine+mitoxantrone+dexamethasone; JC virus, John Cunningham virus; LAMB, liposomal amphotericin B; MCL, mantle cell lymphoma; NR, not reported; PCNSL, primary central nervous system lymphoma; R-bendamustine, rituximab+bendamustine; R-CHOP, rituximab+cyclophosphamide+hydroxydaunorubicin+vincristine+prednisolone; R-EPOCH, rituximab+etoposide+prednisolone+vincristine+cyclophosphamide+hydroxydaunorubicin; R-ESHAP, rituximab+etoposide+methylprednisolone+cytarabine+cisplatin; R-F, rituximab+fludarabine; R-FC, rituximab+fludarabine+cyclophosphamide; WM, Waldenström macroglobulinaemia.

than the mean age of 68 years (range, 49–79 years) of the cases identified in the literature. Six cases were female, 19 cases were male, and the patient's gender was not reported in 15 cases. While our patient's underlying haematological cancer was DLBCL, the cases identified in the literature review had CLL (23 cases), primary central nervous system lymphoma (nine cases), MCL (four cases), or WM (three cases), and one case with both CLL and DLBCL. The vast majority of opportunistic infections were invasive fungal infections, with only one case each of *M. tuberculosis* reactivation and progressive multifocal leucoencephalopathy. A recent *in vivo* study demonstrating increased T lymphocyte numbers and function in patients with CLL receiving ibrutinib therapy may explain why these opportunistic infections are rarely documented in the published literature.[3] The time interval between commencing ibrutinib therapy and the onset of the opportunistic infection ranged from 2 weeks to 2 years. As in our case report, most cases occurred within 6 months of commencing ibrutinib. The most common opportunistic infections were invasive aspergillosis (IA) (19 cases) followed by cryptococcosis (seven cases) and *P. jirovecii* pneumonia (PJP) (seven cases), although a recently published letter reports 13 cases of PJP submitted to the Food and Drug Administration Adverse Event Reporting System.[4] Although it is likely the patient's DLBCL and R-miniCHOP chemotherapy also contributed to his immunocompromise and subsequent pleuropulmonary cryptococcosis, he had commenced cycle 2 of chemotherapy 21 days earlier and he did not exhibit hypogammaglobulinaemia, lymphopenia, or neutropenia. These risk factors for opportunistic infections were reported in only six, two, and three of the literature review cases, respectively, although the majority of cases did not report the IgG level, lymphocyte and neutrophil counts, or lymphocyte subsets. While the case we described received ibrutinib in combination with R-miniCHOP chemotherapy, more cases identified in the literature received ibrutinib monotherapy than combination therapy (21 vs 12 cases). Similar numbers of patients were treatment-naive and pre-treated (16 vs 15 cases). Outcomes were reported in 32 cases. In these cases, mortality attributed to infection occurred in 5/16 (31%) patients with IA, 3/5 (60%) patients with cryptococcosis and 0/5 patients with PJP.

The causal relationship between ibrutinib and IA, an infection typically associated with decreased phagocyte number and function, has been replicated in BTK gene knockout mice. These mice exhibited a significantly higher mortality following *Aspergillus fumigatus* pharyngeal inoculation compared with wild-type mice.[5] Similarly, BTK gene knockout mice exhibited a higher fungal burden than wild-type mice following intranasal, intrathecal and intravenous inoculation with *C. neoformans*.[6] In humans, BTK is expressed by macrophages and neutrophils and activated by binding of fungal components to dectin-1 and toll-like receptor 9, which in turn activate the NLRP3 inflammasome and stimulate production of nitric oxide, proteases, and reactive oxygen species.[7 8]

Although cryptococcosis, particularly *C. neoformans* infection, has traditionally been associated with T lymphocyte immunodeficiency, namely HIV infection and idiopathic $CD4^+$ T lymphocytopenia, and global immune deficits, such as cancer, cirrhosis, diabetes mellitus, glucocorticoid therapy, sarcoidosis, and solid-organ transplantation,[9 10] recent evidence also suggests phagocyte immunodeficiency plays a role in its aetiology. Anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies have been detected in the serum of apparently immunocompetent patients with cryptococcosis in case reports,[11 12] and 4 of 11 patients with cryptococcosis and 7 of 107 patients with *C. gatii* and *C. neoformans* meningitis in observational studies, with or without pulmonary alveolar proteinosis.[13 14] A case–control study detected anti-GM-CSF antibodies in the serum of 1 of 20 healthy Chinese controls and 1 of 21 Chinese cases and 6 of 9 Australian cases of cryptococcal meningoencephalitis, all of which were caused by *C. gatii*.[15] These antibodies are biologically active, inhibiting GM-CSF-induced macrophage inflammatory protein-1α (MIP-1α) expression and signal transducer and activator of transcription-5 (STAT-5) phosphorylation in control peripheral blood mononuclear cells.[13–15] It is plausible that inhibition of phagocyte function by ibrutinib predisposes patients to cryptococcosis as well as IA.

In summary, we report a case in which a 79-year-old man with treatment-naive stage IV DLBCL developed pleural and pulmonary *C. neoformans* infection 6 weeks after commencing treatment with ibrutinib and R-miniCHOP. Although the contribution of the patient's DLBCL and R-miniCHOP to his immunocompromise is difficult to quantify, this case concurs with a growing body of literature describing opportunistic infections, particularly invasive fungal infections, in patients receiving ibrutinib.

Learning points

- Empyema is a rare manifestation of cryptococcosis, which is most commonly caused by *Cryptococcus neoformans* in an immunocompromised host and manifests as an exudative pleural effusion with a lymphocyte-predominant cellular infiltrate.
- A growing body of literature describing opportunistic infections, particularly invasive fungal infections, in patients with haematological cancers receiving the Bruton tyrosine kinase inhibitor, ibrutinib, as monotherapy or in combination with other chemotherapeutic agents suggests a causal association.
- In patients receiving ibrutinib with infections not responding to appropriate empirical antibiotic therapy, invasive fungal infections should be considered, even in the absence of hypogammaglobulinaemia, lymphopenia and neutropenia.
- In vitro studies indicate binding of fungal components to dectin-1 and toll-like receptor 9 activates Bruton tyrosine kinase, resulting in activation of the NLRP3 inflammasome and production of nitric oxide, proteases and reactive oxygen species within phagocytes, implying a mechanism of impaired phagocyte function for the apparent association between ibrutinib and invasive fungal infections.

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Unexpected outcome (positive or negative) including adverse drug reactions