

**Table 1**  
Diagnostic yield for granulomatous inflammation and location of sampling.

Type of procedure	n	Diagnostic yield [n, (%)]
Overall bronchoscopy	40	39 (97.5%)
TBNA alone (per patient)	40	37 (92.5%)
TBNA/station	84	70 (83.3%)
TBNA* Station 2R, 2L	0	NA
TBNA Station 4R	15	10 (66.6%)
TBNA Station 4L	4	3 (75%)
TBNA Station 7	34	30 (88.2%)
TBNA Station 10R	2	1 (50%)
TBNA Station 10L	1	1 (100%)
TBNA Station 11R	9	8 (88.8%)
TBNA Station 11 L	19	17 (83.3%)
Transbronchial lung biopsy	33	10 (26%)
Endobronchial lung biopsy	38	13 (39%)

\*TBNA, transbronchial needle aspiration; Lymph node stations are defined as per IASLC lymph node map.<sup>8</sup>

confirmation of granulomatous inflammation was 92.5% (37/40). TBLB was diagnostic in 2 cases without a TBNA diagnosis. Eighty-four LNs were sampled in the sarcoidosis group. Median number of LN sampled per patient was 2. The diagnostic yield for sarcoidosis per sampled LN was 83.3% (70/84). Station 7 LN was most frequently sampled ( $n = 34$ ) with a diagnostic yield of 88%. The diagnostic yield of various locations and biopsies for sarcoidosis is presented in Table 1. All patients with unexplained benign lymphadenopathy were followed up for at least 6 months.

No procedure related adverse events were noted. One anesthesia related adverse event occurred. We had two instances of sheath breakage from the needle as previously reported<sup>5</sup> without any damage to the bronchoscope.

The current review adds to the growing literature on the utility of EBUS TBNA for establishing the diagnosis of granulomatous inflammation in patients with mediastinal and hilar lymphadenopathy. The randomized controlled studies published using this needle were directed toward malignant lymphadenopathy.<sup>6</sup> Therefore, we would like to share our 3-year experience and diagnostic data with selective use of this needle. The needle is marketed as being more flexible as compared to other needles and authors experience is in-line with prior published reports.<sup>4</sup> We continued to observe a high diagnostic yield for sarcoidosis. However, opposed to our initial findings where we did not see an incremental benefit from TBLB,<sup>5</sup> in this continuation series 2 patients (5%) were diagnosed solely on basis of TBLB. Both these patients had firm LNs with scant aspirate. One patient was clinically diagnosed with sarcoidosis based on response to steroid despite benign cytology and the procedure was considered non-diagnostic.

No patient in this series required additional tissue sampling for diagnosis of granulomatous inflammation. While this review was directed toward sarcoidosis patients, it was noted by the author that many of these patients were referred for evaluation of lym-

phoma given the overlap in symptoms and radiographic findings. We were able to establish a diagnosis of lympho-proliferative disorder in 7 patients but 57% (4/7) required repeat procedures for subtyping.

The sheath breakage events were reported to the manufacturer and no manufacturing defect was identified. In both the instances, lymph nodes were firm and lymph node puncture was deemed challenging. We speculate that the incidents could be related to the excessive torsional strain on the needle.

Since the introduction of this needle, newer needles have been marketed with the promise of providing core specimens. There is a shift toward endoscopic needle biopsy over aspiration in the gastroenterology literature.<sup>7</sup> Similar trend might be noted in pulmonary medicine in coming years as the need for tissue increases. In the absence of comparative data, good performance data and familiarity with design might be a factor for some proceduralists to continue using this needle. It is possible that different attributes of each needle might make them better suited for different pathologies. We share our data to add to the scant available literature about using this needle for granulomatous lymphadenopathy.

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## Invasive Aspergillosis as a Complication of Influenza Virus H3N2 Infection<sup>☆</sup>



### *Aspergillosis invasora como complicación de infección por virus influenza H3N2*

To the Editor,

Invasive aspergillosis occurs frequently in immunocompromised patients, primarily in patients with neutropenia or

individuals receiving treatment with corticosteroids, antibiotics, or cytotoxic drugs,<sup>1</sup> while it is uncommon in patients with preserved cell immunity. Several cases of fungal infection caused by *Aspergillus* have been described in recent years, and this is a complication that should be taken into account in patients who present a pneumonic process during the course of an influenza virus infection.<sup>2</sup>

We report the case of a patient with influenza virus infection who developed invasive aspergillosis as a complication that caused his death.

A 50-year-old patient diagnosed with common variable immunodeficiency receiving treatment with intravenous immunoglobulins every 3 weeks, clinically stable, with no significant infections

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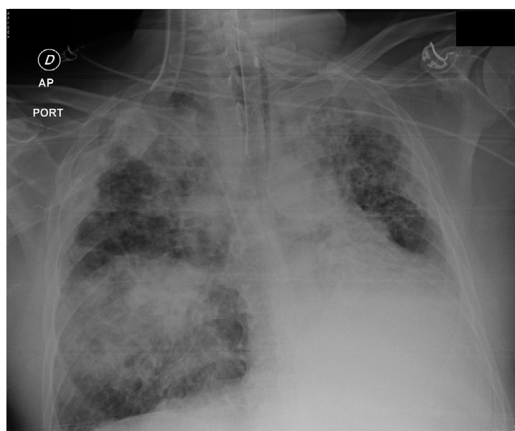


Fig. 1. Right basal lung condensation.

in the last 3 years, consulted his primary care physician with irritative cough, high fever, and dyspnea. He was treated with levofloxacin without improvement, so he attended the emergency room. Physical examination showed BP 133/85, pulse 111 beats per minute, 20 breaths per minute, no fever. Immunoglobulin serum values: IgA: 0 g/l; IgG: 7.05 g/l; IgM: 0.73 g/l. The chest X-ray showed loss of left volume and images of bilateral bronchiectasis without radiological changes. The patient was admitted for respiratory failure. PCR of pharyngeal exudate was positive for influenza virus (H3N2), so treatment began with systemic corticosteroids and oseltamivir, with the addition of piperacillin/tazobactam and intravenous amikacin. After an initial improvement, the patient deteriorated on day 5 of admission with tachypnea, tachycardia, and the appearance of a right basal pulmonary condensation on radiology (Fig. 1), so he was transferred to the intensive care unit, requiring intubation and invasive ventilation. Linezolid and intravenous colistin were added to his regimen. Bronchoscopy was performed, showing images of whitish membranes in the bronchial tree in both sides. Bronchial aspirate and bronchoalveolar lavage showed countless colonies of *Aspergillus fumigatus* and *Aspergillus terreus* sensitive to voriconazole and amphotericin B. Galactomannan testing in bronchoalveolar lavage and blood was negative. Treatment with voriconazole was added, with little improvement. Amphotericin B was then administered, and the patient developed refractory shock and acute respiratory distress syndrome, which caused his death.

The most frequently described complications in patients with influenza virus infection are acute respiratory distress, bacterial superinfection, the selection of oseltamivir-resistant strains, and pulmonary hemorrhage, which can lead to a poor outcome in immunocompromised patients.<sup>1</sup> It is unusual to think of *Aspergillus* as a pathogen capable of causing invasive disease in patients with viral infection, yet since 2010 several cases of influenza virus infection complicated by post-onset invasive aspergillosis have been reported. Influenza virus infection, then, appears to be a new risk factor for invasive fungal infection.

Pathogenesis may be a result of the influenza virus (and the H1N1 virus more frequently) causing severe and diffuse damage to the respiratory mucosa, disrupting the respiratory mucosa, and altering normal ciliary clearance,<sup>3–5</sup> thus permitting invasion by the fungus. The virus can also damage local defenses against *Aspergillus*, alter local phagocytosis produced by alveolar macrophages, and reduce the functionality of natural killer cells and other immune responses.<sup>6,7</sup> A recent publication found that the virus also damages pulmonary and systemic levels of cytokines and the function of pulmonary phagocytes, producing a state of immune deficiency.<sup>8,9</sup>

When influenza virus infection is complicated by fungal co-infection, mortality is approximately 50%–60%, 5 times higher than in hospitalized patients with viral infection only.<sup>3,10</sup> In the series published by Van de Veerdonk et al.,<sup>11</sup> invasive aspergillosis mortality in influenza patients was 55%. Absence of suspicion, the interference of the underlying influenza virus infection, and the limited use of serological diagnostic methods prevent early diagnosis, delay treatment, and lead to increased mortality.

Despite high mortality rates, this association is not routinely reported.<sup>12</sup> The isolation of *Aspergillus* spp. observed in cultures obtained from bronchoscopic samples of patients admitted to the ICU with influenza virus infection can thus be underestimated, and they may be considered contaminants despite their potential to cause invasive disease. The presence of structural lung disease, high doses of corticosteroids, and T cell deficiencies during influenza virus infection may be responsible for an emerging group of patients at high risk of invasive aspergillosis.

According to Wauters et al.,<sup>13</sup> steroid use within 7 days prior to ICU admission was an independent risk factor for fungal coinfection. Patients with influenza treated with corticosteroids before or after admission to the ICU should be carefully evaluated for possible *Aspergillus* coinfection; the authors suggest that systemic steroids should be avoided in patients with influenza, even in those who develop acute respiratory distress associated with their influenza infection.

Our patient had common variable immunodeficiency treated with immunoglobulins, with normal immunoglobulin values except IgA, and no infections in recent years. The infections most frequently described in these patients are bacterial infections (otitis, sinusitis, pneumonia, diarrhea, etc.) associated with humoral immunity deficiencies, which play a lesser role in invasive aspergillosis than the more important cell immunity.<sup>14</sup>

The interest of this scientific letter is that it draws attention to the increased risk of invasive aspergillosis in patients with influenza virus infection (most often H1N1). In patients with worsening symptoms, a chest CT scan and bronchoscopy should be performed early to ensure early diagnosis and treatment of invasive aspergillosis if there are signs indicating its presence. Taking into account the results published in the literature, *Aspergillus* species in the respiratory cultures of critically ill patients, particularly those with influenza virus infection, should not necessarily be considered contaminants or colonizers. Early diagnosis and treatment strategies should be initiated in these patients and multicenter studies should be carried out to better define the incidence and outcome of this disease.<sup>12,15</sup>

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