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CASE REPORT

Companion or pet animals

Disseminated histoplasmosis in an imported Maine Coon cat in western continental Europe

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Abstract

A 4-year-old, male, neutered Maine Coon presented with a 9-month history of weight loss, tachypnoea, dyspnoea and lethargy. The patient had been in the owner's possession since kittenhood in Texas, and 20 months before presentation had moved to Europe, living first in France and then the Netherlands. A bronchoalveolar lavage performed by the referring veterinarian cultured positive for *Mycoplasma* (unknown species), and treatment was initiated with minimal response. Sequential referring radiographs showed progressive diffuse pulmonary broncho-interstitial changes. At presentation, focused echocardiogram suggested moderate likelihood of pulmonary hypertension. Repeat thoracic radiographs showed markedly progressed pulmonary changes, with a new miliary component. Bloodwork showed hypergammaglobulinaemia. Pending additional diagnostic results, the patient passed away within 4 days. Postmortem examination was compatible with severe chronic pyogranulomatous pneumonia with pleuritis, splenitis, hepatitis and adrenalitis, with histopathological identification of intracytoplasmic fungal elements. Sequencing of pulmonary granulomatous tissue confirmed the presence of *Histoplasma capsulatum*.

KEYWORDS

cats, diagnostic imaging, fungal diseases, histoplasmosis, radiography, respiratory disease

BACKGROUND

This case provides an example of an imported domestic animal with extensive travel history presenting with an infectious disease process that is relatively unknown in the countries of destination. *Histoplasma capsulatum* is a dimorphic soil-borne fungus that has a worldwide distribution in temperate and subtropical climates. Historically, it has only been considered as intensely endemic in the midwestern and southern United States and parts of Central and South America.[1–5] However, a recent review recommends broadening the geographic boundaries for endemic histoplasmosis due to increased reports of disease in areas previously considered "non-endemic" (e.g., northern United States, Canada).[6] The review suggests the extent of histoplasmosis may still be vastly underestimated due to misdiagnosis, availability and/or cost of diagnostic tests, and lack of clinician awareness. Additional factors such as increased global movement and climate change are likely contributing to increased cases in "non-endemic" areas.[6]

In Europe, histoplasmosis is still considered to be predominantly imported; however, sporadic reports of suspected autochthonous cases exist, though these predominate in local wildlife in Central Europe with portions of Italy, Germany and Turkey having potentially endemic regions for *H. capsulatum*.[6–8] The few case reports of histoplasmosis in cats in Europe are in those with known travel history.[2,3] While animal histoplasmosis is considered a public health risk due to a potential, theoretical, zoonosis, particularly for immunocompromised humans, there are no known reports of direct animal-to-human transmission. More importantly, infected pets may be a sentinel for human exposure as concurrent infection from a common environmental source has been documented.[4,9,10] With an increasingly international community and importation of domestic animals, it is pertinent for veterinarians to be aware of

any potential infectious diseases from the patient's place of origin.

CASE PRESENTATION

A 4-year-old, male, neutered Maine Coon from the United States (Texas) was referred to the Internal Medicine (Cardiology and Pulmonology) service of the companion animal hospital of Utrecht University, with a 9-month history of progressive weight loss, tachypnoea, dyspnoea and lethargy. Twenty months before presentation, the patient had moved to Europe, living first in France for 14 months and then the Netherlands for 6 months. In Texas, the patient was an indoor/outdoor cat and in Europe it was indoors only.

At 1-year old, in Texas, the patient had radiographs taken for a right forelimb lameness, which showed an incidental pulmonary nodule and moderate to severe interstitial pattern with peri-bronchial changes. There were no respiratory signs at the time, and cytology of the pulmonary nodule was consistent with mild suppurative inflammation. Feline immunodeficiency virus, feline leukaemia virus and heartworm (antigen) tests were negative at the time. The patient was treated with enrofloxacin for 21 days, and no further follow-up diagnostics were performed.

Nine months after moving to France, at approximately 3.5 years of age, the patient developed signs of respiratory disease consisting of intermittent sneezing, purulent nasal discharge, dyspnoea, hyporexia and weight loss (approximately 1.6 kg since the move). Treatment with marbofloxacin was initiated. Two other cats in the same household presented with similar clinical signs; however, these were milder and resolved with antimicrobial treatment. In the case presented here, clinical signs persisted and thoracic radiographs showed a moderate broncho-interstitial pattern and an unremarkable cardiac silhouette. No intra-thoracic lymphadenopathy or pulmonary nodules were identified. A serum biochemistry showed a mildly increased total protein (88 g/dL; reference [ref]: 57–78 g/dL), and complete blood cell count showed mild thrombocytopenia (72 G/L; ref: 200–500 G/I) and lymphopenia (0.8 G/I; ref: 1–7 G/I). The patient's records did not show that the thrombocytopenia was confirmed via a blood smear. Faecal testing performed on a single, 1-day sample (methodology unknown) was negative for parasites. A bronchoalveolar lavage was performed with positive culture results for *Mycoplasma* (unknown species) and unknown cytology results. The patient was started on a course of doxycycline (11 mg/kg per os [PO, orally] every 24 hours), with a mild positive response in the first 2 weeks of treatment with improved appetite and resolved sneezing and nasal discharge. The treatment course was extended, and at the 4-week recheck minimal clinical improvement was noted with repeat radiographs showing static pulmonary changes. Throughout the treatment period, there was persistent dyspnoea and no weight gain. No additional diagnostics were performed, and repeat doxycycline treatments were prescribed for the remaining residence in France.

Further rechecks were performed by the referring veterinarian after the patient moved to the Netherlands. Eight weeks after the initiation of doxycycline treatment, the patient had persistent dyspnoea, and repeat radiographs were similar to the prior study. The owner reported mild hyporexia that resolved with discontinuation of doxycycline. Inhalational corticosteroids were started with fluticasone propionate (one to two inhaled doses twice per day; concentration unknown), though these were discontinued when the patient became anorexic and no improvement in respiratory status was noted. The following recheck was 6 months later, with progressive weight loss, dyspnoea, tachycardia and abnormal lung auscultation. Prednisolone (tapering course started at 1 mg/kg PO every 24 hours) was started, and the patient was referred for further work-up to the companion animal hospital of Utrecht University. The patient received prednisolone for 1 week before presentation, where the owner reported mildly improved respiratory signs and improved appetite. At no point throughout this period was the patient febrile.

On presentation, the patient was quiet, alert and responsive, with marked tachypnoea (100 breaths per minute) and dyspnoea characterised by pendulous abdominal breathing. The patient was underweight (3.8 kg; initial adult weight 7.2 kg) with an unkempt, dull coat, non-febrile, normocardic (180 beats per minute) with strong synchronous pulses, and pale pink mucus membranes. Slight inspiratory stridor was present. Auscultation of the heart was unremarkable, and lung sounds were diffusely increased with harsh expiratory and inspiratory noise.

LEARNING POINTS/TAKE-HOME MESSAGES

- Histoplasmosis has a worldwide distribution and is endemic in many temperate and subtropical climates. Recent evidence suggests that the geographical boundaries are more extensive than historically considered.
- A patient's travel history should be in the medical record, as it will be critical to consider potential exposure to endemic infectious diseases when formulating differential diagnoses.
- Thoracic radiographs of feline histoplasmosis frequently show a diffuse fine or linear interstitial pattern that may have a miliary or nodular component. Intra-thoracic lymphadenopathy is not a key radiographic feature in contrast to dogs.
- Histoplasmosis is most often diagnosed through identification of the organism on cytology or histopathology. Urine antigen testing is becoming increasingly popular, but is not yet widely available. Direct *Histoplasma* spp. polymerase chain reaction or fungal sequencing on tissues is often available through human laboratories.

INVESTIGATIONS

A focused echocardiogram was performed because of the patient's respiratory status. Throughout the scan, there were diffuse B-lines, further limiting evaluation. End-diastolic septal flattening and dilated main pulmonary artery and branches indicated an intermediate probability of pulmonary

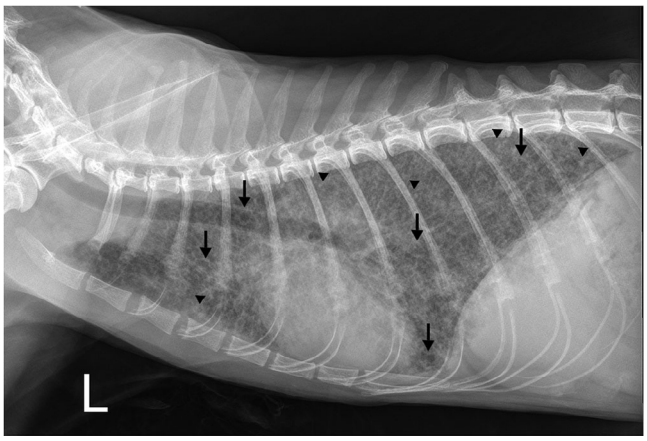

FIGURE 1 Left lateral thoracic radiograph showing the severe and diffuse broncho-interstitial pattern. Throughout the pulmonary parenchyma, multiple small nodular-like lesions compatible with a miliary pattern (arrowheads) are identified, as well as multiple round lucent lesions with a thin soft-tissue opacity rim thought to represent bronchiectasis or air-trapping (arrows).

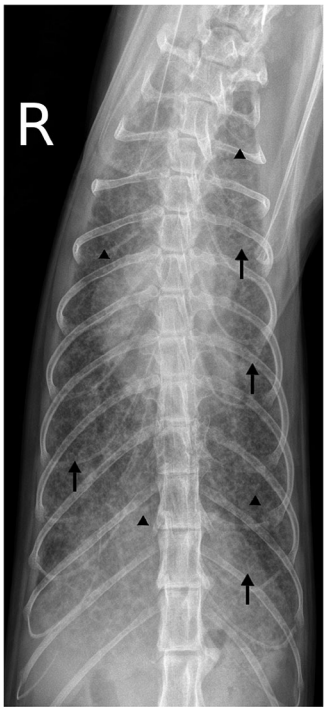

FIGURE 2 Dorsoventral thoracic radiograph showing the severe and diffuse broncho-interstitial pattern. Throughout the pulmonary parenchyma, multiple small nodular-like lesions compatible with a miliary pattern (arrowheads) are identified, as well as multiple round lucent lesions with a thin soft-tissue opacity rim thought to represent bronchiectasis or air-trapping (arrows).

hypertension, based on criteria used for dogs.[11] No other significant echocardiographic abnormalities were identified, and no adult heartworms or pleural effusion were observed.

Repeat thoracic radiographs (Figures 1 and 2) were performed showing a progressive, severe and diffuse broncho-interstitial pattern with reticular and miliary components. Throughout the pulmonary parenchyma, there were multiple round lucent lesions with a thin soft-tissue opacity rim suggestive of bronchiectasis or air-trapping. Due to significant border effacement, assessment of the remaining intra-thoracic structures was limited. Mild cardiomegaly was present with widening at the cranial aspect and increased sternal contact. The pulmonary vessels could not be identified. The diaphragm did not appear tented or flattened. The liver was mildly enlarged, and there was the impression of mild peritoneal effusion. The patient had a poor body habitus, and multiple open physes were still visible.

Serum biochemistry revealed elevated total protein (97 g/L; ref: 54–70 g/dL), elevated gamma globulins (4.1 g/dL; ref: 4.0–8.0 g/dL) and decreased total calcium (2.35 mmol/L; ref: 2.36–2.86 mmol/L). Serum albumin was within reference range (31 g/dL; ref: 25-34 g/dL). Lymphopenia (1800, ref: 2000–7200) was present on a differential white blood cell count. Heartworm antigen testing was negative.

Acquisition of thoracic radiographs and blood sampling resulted in a deterioration in the patient's respiratory status; therefore, additional diagnostics, including an abdominal ultrasound, were postponed. Collection of faeces from 3 consecutive days was recommended to test for respiratory parasites.

DIFFERENTIAL DIAGNOSIS

A chronic infectious process was prioritised as the primary differential category based on evaluation of the serum protein spectrum, travel history, non-specific clinical signs and progressive pulmonary parenchymal changes. Within this category, emphasis was given to fungal, parasitic and protozoal diseases. Histoplasmosis was considered a likely differential for fungal aetiology due to known travel history (Texas), chronic non-specific signs, and the pulmonary nodule identified radiographically in Texas. Parasitic disease (e.g., lungworm, heartworm) was not excluded due to incomplete diagnostic testing history and possible broad radiographic presentation. Protozoal disease (e.g., toxoplasmosis) was also included due to non-specific signs; however, the severe radiographic features in our case are not common for this disease. A degree of chronic changes, such as pulmonary fibrosis, was suspected to be contributing to the patient's radiographic changes. However, this was considered more likely to be secondary to an underlying process and not a primary aetiology. Inflammatory disease (e.g., feline asthma, chronic bronchitis with mucus plugging) was additionally included due to chronicity of non-specific respiratory signs. Complication with doxycycline-resistant *Mycoplasma* infection was also considered possible. As the bronchoalveolar lavage results were incomplete, with only a known bacterial culture and unknown cytology, our considered differentials list was quite broad and included a variety of chronic infectious and inflammatory aetiologies. Due to the patient's slow clinical progression, neoplasia, such as pulmonary lymphoma or diffuse bronchoalveolar carcinoma, was considered unlikely but could not be excluded.

TREATMENT

Hospitalisation and additional diagnostics (e.g., abdominal ultrasound) were offered, but declined by the owner seeing the chronicity and relative stability of the clinical signs.

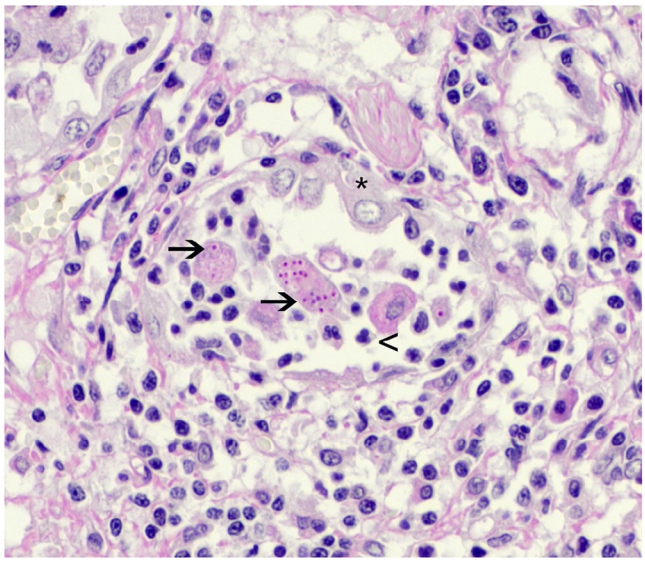

FIGURE 3 Histological picture of the lung. Visible is an alveolus, which has partly lost its epithelium and is partly covered by type 2 pneumocytes (*). Within the alveolar space are neutrophils (<) and macrophages with intracellular *Histoplasma capsulatum* yeast (arrows). Periodic acid–Schiff stain; 400×.

The patient was discharged pending diagnostic results to further determine follow-up options for diagnostics and treatment. The course of prednisolone was continued due to the patient's reported positive response. Albuterol aerosol (100 μg/dose, one inhaled dose every 2 days) was added for broncho-dilatory effects.

OUTCOME AND FOLLOW-UP

Four days after discharge, the patient passed away at home. A postmortem examination was performed, where multifocally, a severe, chronic pyogranulomatous inflammation was identified in the lungs, pleura, liver, spleen, kidney and adrenal glands. The patient only had one kidney. Chronic mild lymphocytic myocarditis was identified in the heart. Intracellular and extracellular fungal elements compatible with *H. capsulatum* were identified in the lungs, pleura, liver, spleen, kidney and adrenal glands. These appeared as 1–4 μm round to oval fungal elements, with a clear 1 μm halo and basophilic centre (Figure 3).

Pulmonary tissue samples were submitted for further confirmation of *H. capsulatum* via sequencing. For DNA extraction, mashed pulmonary tissue was dissolved in 1× TE buffer (Merck). DNA was extracted and purified with the MagNA Pure 96 instrument following the manufacturer's instructions and the Pathogen 200 SV protocol with the MagNA Pure and Viral NA Small Volume Kit (Roche Diagnostics). A polymerase chain reaction (PCR) amplifying the internal transcribed spacer (ITS) and large subunit genes in monoplex was used for subsequent species identification using primers ITS 1 5′-TCCGTAGGTGAACCTGCGG-3′, ITS 4 5′-TCCTCCGCTTATTGATATGC-3′, NL1 5′-GCATATCAATAAGCGGAGGAAAAG-3′ and NL4 5′-GGTCCGTGTTTCAAGACGG-3′.[12,13] PCR was performed on a thermocycler (Biometra, Westburg). Amplicons were purified following the AmpliClean method (NimaGen), and the sequencing PCR was performed using 0.5 μL BrilliantDye premix, 1.75 μL BrilliantDye 5× sequencing buffer (NimaGen), 1 μL ITS 4 or NL4 primer (5.0 μM), 5.75 μL water and 1 μL purified DNA. Afterwards, products were purified using the D-Pure purification protocol (NimaGen) and sequenced on a 3500 XL genetic analyser (Applied Biosystems). Resulting sequences were compared with the NCBI GenBank sequences using the BLAST program (http://www.ncbi.nlm.nih.gov/) to determine species identity, which confirmed the presence of *H. capsulatum*.

DISCUSSION

Histoplasmosis is reported as the second most common systemic fungal disease in cats and has variable disease presentations that include subclinical, granulomatous pulmonary, primary gastrointestinal and disseminated forms. Disseminated forms may include cutaneous lesions and/or osteomyelitis.[1,2,4,5,10,14,15] The majority of infections are often latent or clinically silent. When clinical signs occur, chronic and non-specific signs predominate, such as lethargy, weakness, hyporexia, weight loss and fever. Other clinical signs (e.g., respiratory) are dependent on the extent and location of disease.[1,2,4,5,10,14,16–18] Immunosuppression may result in reactivation of a latent infection; therefore, travel history does not need to be recent. In a prior study of histoplasmosis in 96 cats, 15% had concurrent infection with feline leukaemia virus.[19] Chronic corticosteroid administration has been associated with some clinically relevant feline histoplasmosis cases, likely due to secondary immunosuppression allowing for reactivation of disease.[1] Treatment of histoplasmosis consists of prolonged administration of an antifungal, usually from the triazole-class (e.g., fluconazole, itraconazole), with an average treatment time of 6 months.[1,5,10,16,20] Negative prognostic indicators include clinical variables indicative of severe respiratory, hepatic, haematological or neurological disease.[16,20]

Clinicopathological abnormalities are similarly non-specific, with variable degrees of anaemia, neutropenia, thrombocytopenia, hypoalbuminemia, hyperglobulinemia, azotaemia, hyperbilirubinemia and/or elevated liver enzymes. Hypercalcaemia is occasionally reported and likely related to the granulomatous inflammation.[1,4,5,14] In our case, non-specific bloodwork abnormalities were similarly present. While total calcium was mildly decreased, we lacked ionised calcium, which would have better indicated if there was true clinical hypocalcaemia.

Thoracic radiographs in feline histoplasmosis are frequently abnormal, with pulmonary changes in 87% of one study of 31 cases and 100% of another study with 18 cases.[1,21] Changes generally consist of a fine, diffuse or linear interstitial to broncho-interstitial pattern. A miliary or nodular component may be present. Diffuse alveolar infiltrates or pulmonary consolidation can also be seen. Interestingly, cats do not often show intra-thoracic lymphadenopathy, which is a common finding in dogs.[1,4,5,21]

Diagnosis of histoplasmosis is most often through identification of the organism on cytology or histopathology. Cytological options are numerous including fine-needle aspirates (e.g., lymph nodes, lung, liver, spleen), skin impression

smears, bone marrow aspirates, cavitary effusions, rectal scrapings and tracheal wash or broncho-alveolar lavage fluid. As in our case, oval or round yeast-like cells (2–5 μm diameter) with a central, lightly basophilic body surrounded by a clear halo are most often identified within epithelioid macrophages, though some of the fungal organisms may be free within the pyogranulomatous exudate. Fungal culture is not recommended due to infection risks for laboratory personnel, cost and long incubation period.[1,4,5,10,16,17] Urine antigen tests manufactured and validated for human usage are increasingly being utilised for veterinary patients and appear to demonstrate good reliability, with one study reporting an overall sensitivity of 94.4% in 18 cats with confirmed histoplasmosis. These same tests also represent a non-invasive means of monitoring response to treatment and evidence of disease remission.[15,18,22–26] Historically, serology has been considered unreliable in veterinary patients due to frequent false-positive and false-negative results.[1,5,10,16,26] However, a recent study comparing enzyme immunoassay and immunodiffusion for the detection of anti-*Histoplasma* antibodies found that enzyme immunoassay can provide an acceptable diagnostic performance in the detection of antibodies in the serum of cats and dogs.[26] As recommended by the authors of that study, enzyme immunodiffusion can be considered in situations where histoplasmosis is suspected, but no to little antigenuria is present. The same study found that immunodiffusion, which is what has been historically used by veterinary diagnostic laboratories, has an unacceptably low diagnostic sensitivity and should not be used.[26]

In our case, a broncho-alveolar lavage had been performed by the veterinarian in France, but unfortunately the cytological samples and final report were not available for review. Based on the available medical records, it is assumed that *Histoplasma* was not identified in the sample, and this could have been due to a number of reasons. First, the sample may have been of a non-diagnostic quality (e.g., low cellularity). Second, the individual evaluating the cytology may have failed to recognise the organism either due to lack of knowledge or poor sample preparation, as the organism can be difficult to identify with regular stains.[10] Lastly, it has been reported in other species that chronic respiratory cases may have a lower disease burden, which results in increased difficulties in organism detection. While this has not been reported in cats, it cannot be excluded that this could have occurred with the chronicity of the current case.[1,4,5] Due to the high anaesthetic risk, a repeat bronchoalveolar lavage would have been recommended in our patient only if less invasive tests would be inconclusive. An abdominal ultrasound could have disclosed changes that would have warranted attainment of fine-needle aspirates and possibly reaching a definitive diagnosis considering the pathology results. Unfortunately, this was not performed at the time of presentation, as the cat was not deemed stable enough to tolerate prolonged recumbency. Possibilities for *Histoplasma* antigen testing were still being evaluated at the time the patient died. PCR represents additional confirmatory testing that can be performed, preferentially on fresh tissue samples, and in human medicine can be utilised for providing epidemiological insights.[7,27] PCR is not frequently used in veterinary medicine, likely due to cost, availability, ability to identify the organism on cytology/histology and growing availability of antigen tests.[1,4,5,10]

This case reminds us that imported domestic animals may carry endemic diseases that are relatively unknown in the destination country. Travel history must be taken into consideration when formulating differentials for such a patient, as otherwise the chosen clinical treatment course may be inappropriate. *Histoplasma* represents an important public health matter, as infected animals can act as a sentinel for human exposure, particularly relevant in immunocompromised individuals.[4,9,10]

AUTHOR CONTRIBUTIONS

Elisabeth M. Burgers was the primary author of the manuscript and prepared the initial draft and included figures. Stefanie Veraa was the supervising radiologist for imaging interpretation. Giorgia Santarelli was the primary clinician for management of the case. Wilhelmina Bergmann was the primary pathologist and prepared tissue samples for submission for sequencing. Eelco Meijer performed the confirmatory genome sequencing. All authors contributed to the writing and editing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

The study did not require any institutional or national ethical committee approval as the diagnostic studies and initiated treatments were part of clinical activity. Throughout all examinations and diagnostics, the patient was treated ethically.

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IMAGE QUIZ

Image quiz pertains to Figures 1 and 2.

A 5-year-old, domestic shorthair from the Gulf Coast of the United States had thoracic radiographs performed due to a 9-month history of respiratory signs. A severe and diffuse broncho-interstitial pattern with numerous small soft-tissue opacity nodules throughout the parenchyma (miliary) was present, as well as multiple round radiolucent lesions with a thin soft-tissue opacity rim. There is no indication of pulmonary hyperinflation, and the remaining intra-thoracic structures are overall unremarkable.

MULTIPLE-CHOICE QUESTION

What differential diagnosis should be considered based on the patient's history and radiographic findings?

POSSIBLE ANSWERS TO MULTIPLE-CHOICE QUESTION

A. Metastatic neoplasia
B. Cardiogenic pulmonary oedema
C. Pulmonary haemorrhage
D. Fungal pneumonia
E. Smoke inhalation

CORRECT ANSWER

D. Fungal pneumonia.

Knowing a patient's precise travel history allows further investigation to possible infectious diseases they may have been exposed to. In this case, the patient has a travel history to the southern United States, which is highly endemic for certain fungal diseases, including histoplasmosis and blastomycosis. Further research can be done to determine clinical features (i.e., presenting signs, radiographic changes) associated with these diseases, as well as available diagnostic and therapeutic options. In this case, the travel history, chronicity of disease and pulmonary changes means that fungal pneumonia should be considered as a possible differential diagnosis.