62-year-old woman with PET-positive solitary pulmonary nodule

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DESCRIPTION

A 62-year-old woman was referred to the pulmonary office for an incidentally identified solitary pulmonary nodule. The patient underwent CT of the abdomen and pelvis for evaluation of epigastric abdominal pain and was found to have a pulmonary nodule in the lateral segment of the right middle lobe (RML). Her medical history was significant for hypertension. She reported bronchitis-like symptoms characterised by cough, sputum production, low-grade fever and malaise several months ago, which resolved over a few weeks. At the time of evaluation, she denied any systemic or respiratory symptoms. She was a never smoker and worked as an ophthalmology nurse practitioner. She had no history of tuberculosis (TB) or known exposure to patients with TB. She never travelled outside the USA but lived in a *Histoplasma* endemic rural midwestern state. She was a never smoker and had no pets at home. Her physical examination was completely normal. A dedicated CT scan of the chest demonstrated a mildly irregular, non-calcified 1.4×1.0 cm subpleural pulmonary nodule in the RML (figure 1A). There was no hilar or mediastinal lymphadenopathy. A whole-body positron emission tomography (PET) scan revealed a hypermetabolic RML lung nodule with a standard uptake value of 3.6 (figure 1B). There were no hypermetabolic intrathoracic lymph nodes or evidence of extrathoracic disease.

A CT guided core needle biopsy of the nodule was performed. Histopathological analysis showed a parasite with a thick multi-layered cuticular layer measuring 85 µm in cross-sectional diameter, lodged in a small pulmonary artery branch (figure 2A). A detailed analysis of the parasitic morphology was limited due to advanced decomposition. There was lymphocytic infiltration of the vessel with disruption of the endothelial layer. Perivascular granulomatous inflammation was also seen. Given the presence of the thick cuticular layer, the parasite was thought to be *Dirofilaria immitis*. The filaria IgG4 antibody, measured by ELISA, was obtained to assist with diagnostic certainty. The serological assay showed a high antibody level but still within equivocal range (IgG4 antibody 2.7, negative test <1.5, positive test >3). Based on the compatible clinical presentation, the morphology of the degenerated parasite and equivocal serological assay, the patient was diagnosed with human pulmonary dirofilariasis (HPD) and managed conservatively. A repeat CT scan approximately after 1 year revealed a reduction in the size (1.1×0.9 cm) and the solidity of the nodule (figure 2B).

HPD is a zoonotic disease caused by the parasite *D. immitis*, also known as dog heartworm. HPD is a global disease, but the true incidence and prevalence are unknown.¹ Several reasons contribute to the difficulty in the true estimation of the disease burden. First, many patients with HPD are asymptomatic, and the reported cases used for retrospective analysis may only represent the 'tip of the iceberg'.² Second, not all individuals exposed to *D. immitis* develop a pulmonary nodule or may develop transitional nodule, leading to a false estimation of true prevalence.³ Third, an accurate diagnosis of HPD may be missed unless carefully sought after.^{4,5} Serological evaluation of a population may provide a more accurate approximation of true prevalence, but large-scale seroepidemiological testing is challenging in the absence of commercially available diagnostic tests. Based on available serological data, the prevalence of HPD is likely higher than previously thought, and the seropositivity rate in humans roughly corresponds to that of canine hosts in an endemic area.^{1,6} In the USA, the disease appears to be more common in the Southeastern states along the Gulf and Atlantic coasts.⁷ Domestic and wild dogs are the primary definitive hosts, and the female mosquitoes of several species act as a vector. Other definitive hosts include jackals, coyotes and wolves. In definitive hosts, *D. immitis* causes cardiopulmonary dirofilariasis, which can be a fatal condition. Humans are incidental hosts.

The life cycle of *D. immitis* is composed of a definite vertebrate host and a vector. The vector deposits the infectious larval form, L3 in the wound of the definitive host during a blood meal. The L3 larval form subsequently moults into L4 and L5 (preadult form) within 50–70 days after infection. The preadult parasites invade the capillaries in the subepidermal layer. Due to the thinness of the membrane, the parasite commonly invades the venous side of the capillary bed to enter the circulation. However, the parasite might also gain access to the vasculature through the arterial side.⁸ The preadult worms are detectable in the right ventricle and pulmonary circulation 70–85 days after infection. The parasite reaches sexual maturity in approximately 4 months after the inoculation and able to produce microfilariae (L1) about 6–9 months after infection.¹ The subsequent development of L1 to infectious L3 form occurs in the vector after a blood meal from an infected host. In humans, the development of the preadult parasite into adult worms is arrested. The preadult worms can reach the right ventricle and pulmonary

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Figure 1 Axial computed tomography (CT) of the chest revealed mildly irregular subpleural pulmonary nodule in the lateral segment of the right middle lobe (A). There was mild pleural thickening (arrow) adjacent to the lesion. B) Positron emission tomography (PET) scan showing hypermetabolic RML (arrow) nodule with a standard uptake value (SUV) of 3.6.

artery but do not develop into sexually mature form capable of producing microfilariae.

HPD typically presents as an incidentally identified pulmonary nodule on imaging and often raises concern for pulmonary malignancy. In a minority of patients (up to 40%), an acute pneumonitis picture may be seen.^{9 10} These patients become symptomatic during the acute phase of the disease when the worm gets lodged in small pulmonary artery branches causing vascular occlusion and pulmonary infarction.^{11 12} The mechanical irritation from the parasite and moulting fluid may cause endothelialitis, periarteritis and haemorrhage in the vessel wall.⁸ These causes damage to the vessel wall leading to oozing of intravascular content into the perivascular space and development of interstitial oedema. The interstitial fluid may reach the pleural space causing pleural effusion.¹³ The parasite may also escape to the perivascular space and subsequently lead to the development of granulomatous inflammation. Humans mount an exuberant immunological response to the parasite leading to the eventual destruction of the parasite. Development of pulmonary nodule is the end result of the inflammatory cascade. The acute phase may be characterised by fever, cough, sputum production, chest pain, wheezing, haemoptysis and malaise. Chest radiology typically demonstrates patchy, non-nodular opacity.

Figure 2 (A) Histopathological analysis of the core needle biopsy of the pulmonary nodule showed a parasite with thick multi-layered cuticle lodged in the small pulmonary artery branch (black arrow). The parasite measured 85 µm in cross-sectional diameter and demonstrated advanced stages of decomposition. Degenerating muscular ridges were also seen. The parasitic morphologies were thought to be consistent with *Dirofilaria immitis*. There is lymphocytic infiltrate of the disrupted vascular endothelium. There are areas of necrosis surrounding the lesion. In addition, perivascular granulomatous inflammation was noted (orange arrow). (B) CT chest obtained approximately after 1 year revealed reduction in the size and solidity of the lesion (blue arrow).

The pulmonary nodules in HPD are predominantly solitary (75%–95%).¹⁴ The lesions are of variable size measuring 0.5–4.5 cm.¹⁰ The nodules are more subpleural than central in location and are commonly seen in the right lower lobe (RLL).^{11 15} The RLL predominance is thought to be secondary to a larger surface area and higher blood flow to the RLL compared with other lung lobes. The nodules typically have a smooth border with rare reports of perturbation.¹⁶ Sometimes the nodules can be calcified.⁷ The nodules might persist or disappear over time. The pulmonary nodule in our patient demonstrated hypermetabolic activity on PET scan, a feature that has not been reported in the literature. Three previous cases reported minimal to no 18-fluorodeoxyglucose uptake in the nodule.^{17–19} The PET positivity may also complicate the presurgical differentiation between HPD and malignancy.

The diagnosis of HPD is rarely considered during the initial evaluation of a pulmonary nodule. As a result, HPD is typically diagnosed following histopathological analysis of surgically resected specimen either by video-assisted thoracoscopic surgery or thoracotomy. Fine needle aspirations generally are non-diagnostic; only two other cases except ours have been reported in the literature.^{20 21} The parasite may be difficult to identify on histopathology due to a variable degree of degeneration. *D. immitis* can be seen lodged in a small pulmonary artery branch or in the perivascular space. A thick, multi-layered, smooth cuticular layer may be the only identifiable clue. The presence of thin wall tubules inside the cuticular layer signifies genital and gastrointestinal tracts.²² The arteries may show evidence of endothelialitis, lymphocytic infiltration, intimal hyperplasia and vascular disruption.

Serology and molecular testing may play a crucial role in the diagnosis of HPD. The filarial IgG4 antibody test used for our patient is not specific for *D. immitis*. This ELISA-based test uses a purified antigen from *Brugia malayi* and can identify exposure to *D. immitis*, *Wuchereria bancrofti*, *B. malayi* and *Onchocerca volvulus*. Although not available in commercial laboratories, ELISA using Di22 and a recombinant antigen, beta-galactosidase *D. immitis* recombinant fusion protein, have demonstrated high sensitivity and specificity for the diagnosis of HPD.^{23 24} However, it is crucial to emphasise that the presence of anti-*D. immitis* antibody in the patient's serum indicates prior exposure to the parasite and does not necessarily implicate HPD as the cause of pulmonary nodule. Detection of parasitic DNA by PCR from degenerating parasite on the histopathological specimen may also provide diagnostic certainty. *Wolbachia* is a symbiotic intracellular bacteria that is crucial for the development of the *D. immitis* parasite. Serological testing for anti-*Wolbachia* antibody

Learning points

- ▶ Human pulmonary dirofilariasis (HPD) is a rare zoonotic disease that can present as both pneumonitis or pulmonary nodule.
- ▶ The pulmonary nodule can be positron emission tomography positive.
- ▶ Identification of the parasite may be challenging due to the variable degree of degeneration. *Dirofilaria immitis* can be recognised by the presence of its characteristic multi-layered thick cuticle lodged intravascularly or in the perivascular space.
- ▶ Prelung resection identification of HPD may allow for conservative therapy and avoidance of invasive surgery.

or identification of its molecular components on histopathological samples may also provide diagnostic clues. If a diagnosis of HPD can be made before surgical resection, no specific treatment is required.

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