

IDIOPATHIC PULMONARY CALCIFICATION AND OSSIFICATION IN AN ELDERLY WOMAN WITH A MISSED DIAGNOSIS OF SUBARACHNOID HAEMORRHAGE

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SUMMARY

This is a case of idiopathic pulmonary calcification and ossification in a 70 year old with long-standing diabetes and hypertension. Thirteen years prior to her demise, she was first noticed to have multiple calcific deposits in her lungs on a chest X-ray film. She had no risk factors for soft tissue calcification and ossification. Histology of tissue from autopsy showed intraparenchymal pulmonary calcification and ossification with marrow elements. Idiopathic pulmonary calcification and ossification is rare. At autopsy, she was also found to have had bilateral subarachnoid haemorrhage (SAH), a diagnosis missed during clinical evaluation. We highlight the pertinent details in our patient's management that could have helped to prevent a missed diagnosis of SAH. Even though SAH occurs most commonly following head trauma, the more familiar medical use of SAH is for non-traumatic SAH occurring following a ruptured cerebral aneurysm. This patient had notable risk factors for cerebral aneurysm formation but an aneurysm was not identified at autopsy. The location of the blood high on the cerebral convexities further suggests a traumatic origin rather than a ruptured aneurysm. Heterotopic calcification and ossification (HO) is known to occur in the setting of severe neurologic disorders such as traumatic brain injury but the fact that the lung calcification in our patient predated the brain injury by over 10 years makes it unlikely for the HO to have been due to the brain trauma. Other organ pathologies found at autopsy include chromophobe renal cell carcinoma, renal papillary necrosis, lymphocytic thyroiditis, and seborrheic keratosis.

Keywords: Idiopathic pulmonary calcification and ossification, traumatic subarachnoid haemorrhage.

INTRODUCTION

We present an interesting case with multiple pathologies at autopsy including idiopathic pulmonary calcification and ossification and a traumatic subarachnoid haemorrhage (SAH).

Idiopathic pulmonary calcification is rare.^{1,2} To the best of our knowledge, there have only been 2 reports of idiopathic pulmonary calcification from Nigeria.^{1,2} SAH occurs most commonly following head trauma; however the more familiar medical use of the term SAH is for non-traumatic SAH occurring following the rupture of a cerebral aneurysm.³ There was no clinical suspicion of SAH in our patient. The diagnosis of SAH is too often missed⁴, even by expert physicians and in developed nations hence, we feel the need to highlight the pertinent details in our patient's management that could have helped to prevent a missed diagnosis of SAH.

CASE REPORT

The patient is a known hypertensive diagnosed 21 years before her demise. She was diagnosed with diabetes mellitus 3 years later. Terminally, she presented with sudden-onset altered sensorium and restlessness and she died shortly after presentation and before a CT scan could be done. Significant past medical history was that of a fall 2 weeks previously, CT scan done then showed no significant findings. Following the fall, the patient presented in the hospital with a headache, and this resolved spontaneously within the next few days. There was no loss of consciousness or hemiplegia. Her blood pressure values at both presentations were markedly elevated, with systolic blood pressures over 200mmHg.

Anatomical diagnosis

Elderly woman with mild pallor, moderate peripheral and central cyanosis, raised intracranial pressure secondary to bilateral subarachnoid haemorrhage and cerebral oedema, hypertensive cardiovascular disease

with acute left ventricular failure and chronic venous congestion in the lung, liver and the spleen; severe complicated atherosclerosis of the medium-sized and large vessels; intra-parenchymal pulmonary calcification and ossification, chromophobe renal cell carcinoma and renal papillary necrosis, lymphocytic thyroiditis, and seborrheic keratosis.

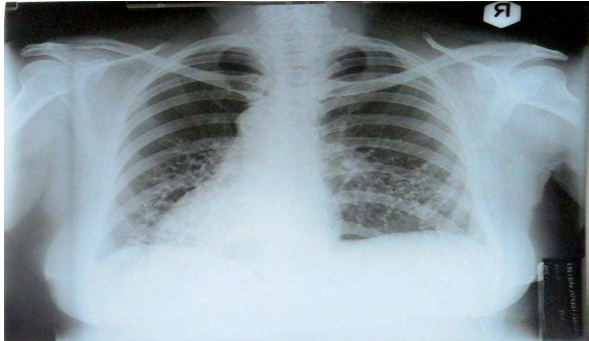


Figure 1 A chest X-ray film showing multiple calcific/ossified deposits in the lung

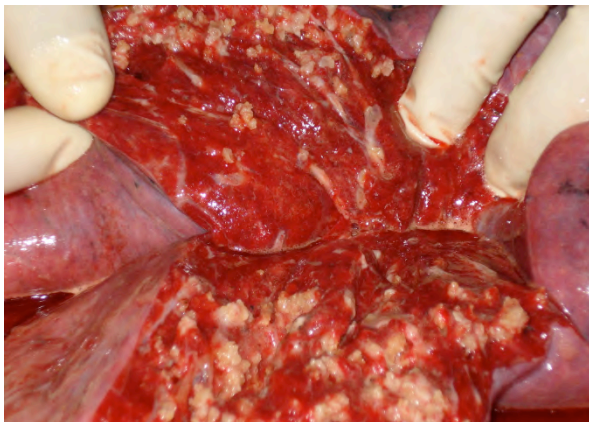


Figure 2 Gross morphology of the lung with multiple hard white deposits within the parenchyma.

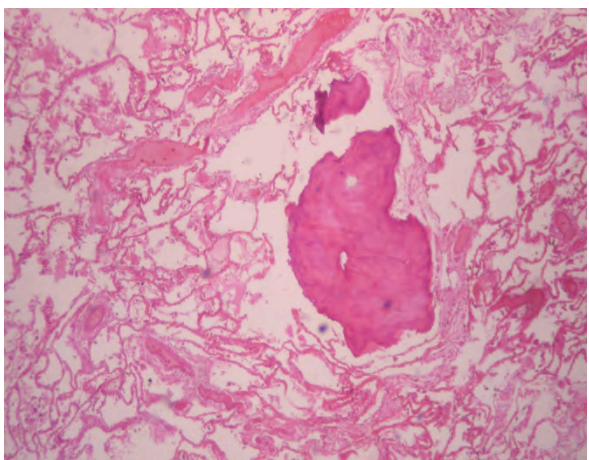


Figure 3 Histological section of the lung showing pieces of woven and lamellar bone within the lung parenchyma (X400)

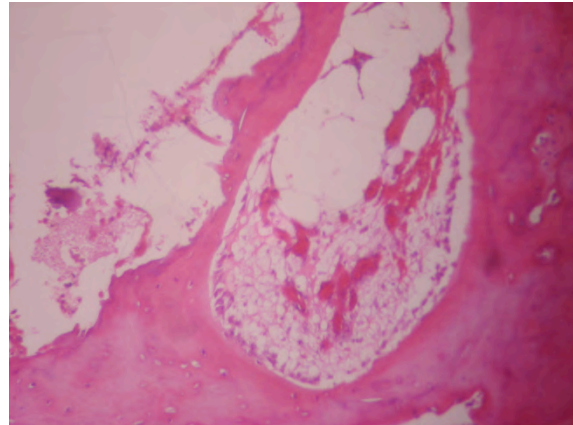


Figure 4 Histological section of the lung showing lamellar bone with associated marrow elements (X800)

Cause of death was determined as raised intracranial pressure resulting from bilateral subarachnoid haemorrhage.

Figures 1 to 4 show the radiograph of the chest, gross and histological findings of the lungs.

DISCUSSION

This patient had none of the known risk factors for soft tissue calcification or ossification. Risk factors for ectopic calcification include haemodialysis for chronic kidney disease; benign causes of metastatic calcification such as orthotopic liver transplantation and primary hyperparathyroidism; malignant causes such as parathyroid carcinoma and multiple myeloma; causes of dystrophic calcification such as granulomatous disorders e.g. tuberculosis, viral infections, parasitic infections, amyloidosis, pulmonary vascular calcifications, coal workers' pneumoconiosis, silicosis; and pulmonary alveolar microlithiasis.⁵

The earliest record of these calcific lung deposits was 13 years before her demise on a routine chest radiograph at a wellness clinic (Figure 1). Calcium levels were never found to be abnormal at the regular checks during this patient's life. Her serum calcium ranged between 2.29 and 2.77mmol/L (Reference range- 2.25-2.75mmol/L). She had no symptoms of lung function compromise at any time. Periodic follow-up with chest radiographs showed no appreciable increase in the size or quantity of these deposits.

Ectopic calcification refers to the deposition of calcium salts in tissues while pulmonary ossification is defined by the presence on histology of mature bone in the lung, with or without marrow elements.⁵ Histology done on patient's lung tissue showed both woven and lamellar bone with marrow elements within the alveolar spaces.

Majority of soft tissue calcifications (more than 95% of cases) are due to dystrophic calcification occurring in damaged tissue in the absence of elevated blood calcium levels.⁶ One per cent to 2 per cent of soft tissue calcifications are due to metastatic calcification occurring in normal tissues in the presence of elevated blood calcium levels.⁶ Even much less common than metastatic calcification is idiopathic soft tissue calcification in which case the aetiology is unknown. A good example is found in pulmonary alveolar microlithiasis (PAM). PAM is a diagnosis of exclusion.⁵

Having excluded all other causes of pulmonary calcification and in view of the typical clinical and radiologic findings in our patient, we submit that she had a mild and slowly progressive form of pulmonary alveolar microlithiasis with ossification. PAM is a rare disorder.^{1,5} It is recognized by the intra-alveolar accumulation of spherical calcified concretions.⁵ Most patients are between 30 and 50 years of age at first presentation⁵ even though a case has been reported in a 6 year old.¹ Common symptoms include cough and dyspnoea.⁵ However, most patients are asymptomatic until late in the course of the disease when severe lung restriction may ensue with impairment of the diffusing capacity and gas exchange abnormalities.⁵ Our patient remained asymptomatic till the date of her demise.

It is known that PAM tends to be familial.^{1,5} Even though there is a familial association in at least 50% of the cases, common environmental factors have also been implicated.⁵ As observed in our patient, the chest radiograph is known to show bilateral, sand-like, micronodular calcified densities known as microliths or calcispherites, which are usually less than 1mm in diameter.⁵ It is speculated that, due to an unknown stimulus, changes in the alveolar lining membrane or secretions result in greater alkalinity, promoting intra-alveolar precipitation of calcium phosphates and carbonates.⁵ An isolated inborn error of calcium metabolism in the lungs has been proposed, but circulating calcium and phosphorus levels are consistently normal in PAM.⁵ There is no evidence that infection plays a role in PAM.⁵

The microliths/calcospherites may serve as a nidus for ossification with the formation of bone occurring by pathways involving one or more growth factors such as Transforming growth factor- β , Vascular endothelial growth factor (VEGF), Interleukin-1, 4 and bone morphogenic protein.⁵ Heterotopic ossification (HO) is defined as the deposition of bone at an abnormal anatomical site, usually in soft tissue.⁷ The aetiology and the pathogenesis of HO remain unknown.⁷

However, clinical and experimental evidence supports the hypothesis that trauma is one of the most important initiating factors⁷. Apart from trauma, heterotopic calcification is known to occur in the setting of severe neurologic disorders such as traumatic brain or spinal cord injury, stroke, encephalitis, polio, tetanus, tabes dorsalis, syringomyelia, anoxic encephalopathy.⁷ There was no history of trauma to the lung in our patient and the fact that this patient's lung calcification predates the brain injury by over 10 years makes it unlikely for the HO to have been due to the brain trauma.

HO may also occur due to genetic conditions such as fibrodysplasia ossificans progressiva and progressive osseous heteroplasia, studies of which provide some insight into the pathogenesis of HO.⁸ In these conditions, there is overexpression of bone morphogenic proteins, overexpression of multiple antagonists of this protein, and mutations in some proteins involved in the signaling pathways for osteogenesis.⁸

This patient was also found to have about 200mls of subarachnoid blood over both cerebral hemispheres. Subarachnoid haemorrhage (SAH) results most commonly from head trauma; of non-traumatic cases, 80% result from ruptured intracranial aneurysms.^{3,4}

Even though this patient had notable risk factors for cerebral aneurysm formation viz. hypertension, atherosclerosis and haemodynamic stress,³ an aneurysm was not identified at autopsy. The location of the blood high on the cerebral convexities further suggests a traumatic origin as blood from a ruptured aneurysm is more likely to be in the basal cisterns.⁴ The initial clinical suspicion in a patient like ours would be a cerebrovascular disease in view of the poorly-controlled hypertension but it is important to note that hypertension is also a strong risk factor for SAH.⁴ Other risk factors for SAH include alcohol (especially a recent binge), cigarette smoking, the use of cocaine and other sympathomimetic drugs, a past or family history of SAH, and some connective tissue disorders.⁴

It is possible that the patient's fall which occurred 2 weeks before her demise was a small undiagnosed SAH associated with the trauma.⁴ If that was the case, the terminal incident was likely a re-bleed. In patients with head injury, a subarachnoid bleed may be traumatic in origin; however, the possibility that a ruptured aneurysm caused the trauma must also be considered.⁴ In other words, the subarachnoid bleed could have been a cause or an effect of the trauma. The diagnosis of SAH is too often missed.

In the United States, approximately 30% of patients with SAH are misdiagnosed at their initial visit to a physician with recurrent bleeding occurring before definitive treatment was commenced.^{4,9} Edlow^{4,9} discusses several reasons for the misdiagnosis of SAH.

A classic case of SAH presents with a severe and distinctive headache, usually with neck pain, vomiting, and transient loss of consciousness.⁴ Physical examination may reveal meningismus, ocular hemorrhages, or any focal or generalized neurological findings.⁴ There are many variations however, and a patient with SAH may present with no significant neurological findings.⁴ Kowalski et al showed that about 19% of the patients in their cohort had normal mental status at first contact.¹⁰ This study also showed that normal mental status, small SAH volume, and right-sided aneurysm location were independently associated with misdiagnosis.¹⁰ Migraine or tension headache (36%) was the most common incorrect diagnosis, and failure to obtain a computed tomography (CT) scan was the most common diagnostic error (73%).¹⁰ Neurologic complications occurred in 22 patients (39%) before they were correctly diagnosed, including 12 patients (21%) who experienced re-bleeding.¹⁰ Patients with an incorrect diagnosis suffered worse outcomes than those with a correct diagnosis at presentation.^{4,9,10} Among patients with normal mental status at first contact, misdiagnosis was associated with worse quality of life at 3 months and an increased risk of death or severe disability at 12 months.¹⁰

Our patient's only symptom after the fall was a headache which resolved spontaneously. Headaches are nearly ubiquitous but one must distinguish those patients with headache caused by SAH (or other serious causes) from those due to self-limited causes.⁴ A CT scan following the fall showed no significant findings.

The sensitivity of CT decays rapidly with time, it is most sensitive within the first 12 hours but even then, the confidence intervals are sufficiently wide that

further testing is recommended in patients with normal CT scans.^{4,9} Routine lumbar puncture is the best way to avoid misdiagnosis in patients with normal scans.⁴ LP is most useful when done within the first 12 hours.⁹

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