Idiopathic Disseminated Pulmonary Ossification*

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Disseminated ossification of the lungs is rare. Most of the cases reported in the literature are associated with mitral stenosis, hemosiderosis and granulomas. Wells and Dunlap,¹ in a review of the literature in 1943, stated that about 45 cases of diffuse ossification of the lung unassociated with tuberculous scars had been reported, of which about 35 cases were of the racemose or branching type. Most of these cases were found in the German literature. A review of the English literature since the article by Wells and Dunlap fails to reveal a single case of disseminated pulmonary ossification of the idiopathic type, that is, pulmonary ossification not associated with mitral stenosis or hemosiderosis.

Even the rarity of disseminated pulmonary ossification associated with mitral stenosis is stressed by several authors.²³ Lawton in England in 1949 was able to collect 40 cases. Wilson, Sasaki and Johnson³ in 1959 were able to find only 23 cases adequately documented by necropsy or lung biopsy. They stated that other cases have been reported on the basis of radiologic examination, but lacked pathologic confirmation. They found only three confirmed cases in the American literature; to this they added four, all associated with mitral stenosis. The case herein reported is one of disseminated ossification of the lungs of the idiopathic type, not associated with mitral stenosis or hemosiderosis.

Report of Case: The patient, a 73 year-old Caucasian man, was admitted to the Harbor General Hospital on three separate occasions, starting in August, 1948. At this time, he had a urethral stricture associated with scrotal cellulitis and perineal fistulae. Dilatation of the urethra and supportive measures were instituted. He was readmitted in November, 1948, when fistulae formation, bilateral orchectomy and scrotectomy were performed. In August, 1952, he was readmitted for the third and last time with the complaints of urinary bleeding, back pain, abdominal pain, chills and fever.

He fractured his right fifth, sixth and seventh ribs about 15 years ago; surgery consisted of closure of chest wound. He stated that he had gonorrhea about 45 years ago. The family history was essentially negative.

The physical examination revealed a well developed and well nourished white man in no acute distress. His temperature was 99°F., pulse 100, respirations 24, and blood pressure 140/80. The thorax was increased in postero-anterior diameter. A scar involved the right chest wall. The lungs were clear. The heart sounds were faint and the rhythm regular. A-2 was greater than P-2. No murmur or thrill was evident. The abdomen was obese and nontender. There was a right direct inguinal hernia and a lower midline cystostomy scar. The testicles and scrotum had been surgically removed. Rectal examination was negative. The lower extremities revealed small varicosities and one plus pitting edema.

The urine was grossly bloody, had a specific gravity of 1.020 and 3+ albumin; microscopic examination showed numerous red blood and white blood cells. A urine culture showed gamma streptococci and coagulase negative Staphylococcus albus.

Hematologic examination revealed hemoglobin 9.5 gm., red blood cells 3,490,000, white blood cells 9,200 with a differential percentage of 18 bands, 40 neutrophils, 36 lymphocytes and six mononuclear cells. The platelets were adequate.

A chest x-ray film on September 2, 1952 revealed callus formation of the fifth, sixth and seventh ribs, in posterior axillary line. Pleural thickening was present in the right base. The left base and sulcus were clear. There was no evidence of infiltration in either lung. The cardiac silhouette was negative.

Cystoscopy revealed a bladder tumor involving the left wall which on biopsy showed an invasive squamous cell carcinoma. On October 7, 1952, a large intravesical tumor of the posterior floor, lateral wall and vault was resected. His postoperative condition was poor; he went into shock and was treated symptomatically. He developed pulmonary edema and expired on October 25, 1952.

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The necropsy revealed a recent transverse suprapubic abdominal incision 5 cm. in length, slightly open, which exuded a small amount of turbid fluid. A small fistula extended from the urinary bladder to the suprapubic abdominal wall. The bladder was adherent to the abdominal wall; the pericystic tissue was hemorrhagic. The urinary bladder contained purulent material and the mucosa of the posterior wall was ulcerated. Microscopically, the bladder wall was invaded by an undifferentiated squamous cell carcinoma. The ureteral orifices were patent. The prostate gland was moderately nodular.

The kidneys were mildly enlarged, each weighing 170 gm. and the capsules stripped with relative ease revealing grayish-tan surfaces from which projected numerous abscesses measuring up to 2 cm. in diameter; some pus was present in the perinephric fat. Microscopically, there were areas of acute pyelonephritis with abscesses and moderate arteriosclerosis. The pelvis and ureters contained cloudy fluid, but were free from other abnormalities.

The heart weighed 360 gm. There was a moderate amount of subepicardial fat. The chambers were patent and the right and left ventricular walls measured 0.3 and 1.2 cm., respectively. The bases of the mitral and aortic valves showed mild sclerotic thickenings. The valves, which had the following measurements, tricuspid 13, pulmonic 9, mitral 12 and aortic 9 cm. in circumference, showed no evidence of rheumatic fever. The coronary arteries were patent and showed mild sclerotic changes. Microscopically, the myocardium of the left ventricle revealed several small areas of fibrosis. There was moderate sclerosis of the abdominal aorta.

The liver weighed 1550 gm. and several capsular fibrous tags were adherent to the diaphragm. The cut sections revealed passive congestion. In addition, on microscopic examination, small foci of polymorphonuclear leucocytes were present in midzonal areas. The gallbladder was moderately distended with bile and contained several stones of the mixed variety. The bile ducts were patent.

The spleen weighed 400 gm. and was adherent by fibrous bands to the diaphragm and stomach. There was a subcapsular abscess measuring 2.5 cm. in diameter; the remainder of the spleen showed an acute splenitis.

Except for dilatation and congestion of the ileum, the gastrointestinal tract revealed no abnormality.

The pancreas revealed a few focal areas of acute inflammation and fat necrosis. There was moderate lipid depletion of the adrenal glands.

The Lungs: The right thorax revealed an old scar extending from the sixth intercostal space in the anterior axillary line to the eighth intercostal space in the posterior axillary line, a distance of 6 cm. There were old adhesions involving the visceral and parietal pleura of the lower lobe of the right lung; a few old adhesions involved both apices. In both lower lobes and in the left upper lobe, there were numerous scattered subpleural bone spicules measuring up to 0.3 cm. in length; most of the spicules measured 0.2 to 0.3 cm. These spicules were incorporated, in many instances, within the lung parenchyma, for a distance of 3 to 4 cm. from the pleura and several involved the interlobar septae. Uninvolved lung parenchyma separated spicules of bone. Many of the bone fragments had sharp ends and shelled out easily. No bone was found in

FIGURE 1: Bone spicules in subpleural alveoli. (H. and E. X60)
the adhesions of the apices. The lungs otherwise showed moderate emphysema of all lobes, with small scattered areas of bronchopneumonia. The lower lobes were congested.

Microscopically, there were many scattered spicules of bone underlying and within the moderately thickened visceral pleura, and occupying distended alveolar spaces (Fig. 1). The alveolar septa were thin-walled or moderately thickened and frequently ruptured. The spicules contained islands of hemopoietic marrow (Figs. 2 and 3). These islands were extremely cellular and had occasional magakaryocytes. Nowhere were there islands of undifferentiated mesenchyme, nests of granulation tissue and hemosiderocytes upon which bone may be formed, or immature bone of the woven type. In essence, the bone was of the mature type without evidence of immature bone formation.

**Discussion**

Disseminated ossification of the lungs is classified into two forms: (1) nodular circumscribed and (2) racemose or branching, or trabecular. These are differentiated anatomically and in the kind of patients involved.

The nodular circumscribed form chiefly affects young people with mitral stenosis. Most of the cases observed have been in men under the age of 40, with an occasional patient between 40 and 50. These patients had advanced cardiac disease, almost exclusively mitral stenosis, with accompanying congestive failure. Radiologic examination showed the characteristic findings of mitral stenosis and many discrete opacities throughout the lung fields, but mainly involving the lower lobes, especially the right. The bony nodules at necropsy were discrete, widely scattered throughout the lungs, usually subpleural, and in the form of small, flat or oval plaques measuring from 2 to 8 mm. These nodules appear to be the result of connective tissue proliferation, following the organization of chronic pulmonary passive congestion or interstitial pneumonitis, producing a bony metaplasia.

The branching or trabecular form, on the other hand, almost invariably involves men of advanced years. Daust found the average age of patients having this form to be 67 years. Approximately 30 per cent of the cases collected by Daust (7 of 23 patients) had cardiac disease of the arteriosclerotic type; none had evidence of mitral stenosis. The bone lesions have been described as consisting of branching spicules of true bone, deposited in the septums of the lungs, often continuous for some distance but with isolated spicules. The process is usually more localized than the nodular circumscribed form. The bone spicules are considered to result from metaplasia of senile alterations of perivascular connective tissue. Osteoid tissue is laid down in the vascular connective tissue and is then converted to true bone. Marrow formation is occasionally observed, but not nearly so frequently as that found in bone resulting from calcification of tuberculous scars or ossified bronchial cartilage.

In the case herein reported, the patient was an elderly man who had evidence of mild arteriosclerotic heart disease, involving mainly the base of the mitral and aortic valves, but without evidence of rheumatic endocarditis. Cardiac failure was of a mild degree, as revealed by passive congestion of the lower lobes of the lungs. The patient, furthermore, had not succumbed to cardiac failure, but to a septicemia, resulting from an ascending pyelonephritis, following a partial resection of an invasive squamous cell carcinoma of the urinary bladder.

**FIGURE 2**

**FIGURE 3**

**FIGURE 2:** Mature bone spicule with marrow within alveoli. (H. and E. X90). **FIGURE 3:** Bone marrow of spicule of Figure 2. (H. and E. X500).
The old trauma of the right thorax had produced scar tissue and pleural adhesions of the lower lobe of the right lung. Bone, however, had not occurred in these tissues and it was more pronounced in the opposite lung.

The characteristic bone lesions were laid down in subpleural fibrous tissue and in intra-alveolar spaces; an occasional bronchial cartilage plate was ossified. The bone was in the form of mature trabeculae, having cement lines, osteocytes and ill defined osteoblasts. Most of the spicules had well defined marrow with myeloid and erythroid elements and occasional megakaryocytes. The bone being of small size, mainly under 5 mm. in length, was not visible roentgenologically. Nowhere was immature woven bone seen. The bone, hence, gave the impression of having been present of long duration.

The pathogenesis of idiopathic pulmonary ossification, and for that matter, of pulmonary ossification associated with mitral stenosis, is obscure. It is known that mesenchymal tissue, rich in proliferative connective tissue and blood vessels, is the framework upon which bone is formed. This tissue may form in areas of organizing chronic passive congestion, and of pneumonitis. Calcified woven bone appears first, and upon this structure, bone is built and replaced by the maturer lamellar bone. Later myeloid conversion occurs, once maturity and stability of the bone is achieved. Hence, the maturity of the bone formed may depend on the duration of the development of the bone. In those patients who die from mitral stenosis, younger bone forms are usually seen, since the bone may have insufficient time to become mature.

Other factors, however, besides chronic passive congestion and its framework of mesenchymal tissue, must be present before bone develops in the lung, since bone is uncommon in cardiac failure, even of long standing. Orishman and Kane, in discussing the origin of bony nodules associated with mitral stenosis, state that since the lesions were already established before any clinical congestive failure appeared, the precursor to these lesions must appear early in rheumatic fever and probably in childhood. Factors other than, or in addition to, vascular congestion must be involved even though the distribution of the nodules at the bases favor congestive failure and their sequelae. Such factors, however, are unknown.

It is possible that some pulmonary bone spicules may result from the development of intrapulmonary embryonic mesenchyme. In the development of the lungs in the embryo, as the lungs invade the spongy mesenchyme of the body wall, and are surrounded by the developing ribs, it is possible that some mesenchyme or rib anlage may become engulfed in the developing lungs. This tissue may then remain as embryonic remnants and under proper stimuli, subsequently develop into rudimentary ribs or bone trabeculae. In this way, then, some cases of pulmonary ossification, in which pulmonary congestion and pneumonitis are of a minor degree and of short duration, could be explained.

REFERENCES


PAPILLIFEROUS TUMORS OF THE HEART VALVES

Two papilliferous tumors of the semilunar valves are described. One occurred on the pulmonary valve of a man aged 57 years and gave rise to no symptoms. The other grew on the anterior cusp of the aortic valve of a woman aged 45 years. This partially filled the anterior aortic sinus close to the ostium of the right coronary artery and was associated with angina pectoris during life.