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CASE REPORT

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A Soft-Tissue Calcification: Differential Diagnosis and Pathogenesis

ABSTRACT: An autopsy of a 72-year-old white male revealed a 30.5 × 5.1 cm vertically aligned heterotopic ossification just deep to a 30.5 cm midline abdominal scar. The ossified mass was determined to be a heterotopic ossification or myostitis ossificans (MO) traumatica resulting from an abdominal surgical incision during life. While, MO traumatica is relatively common accounting for roughly 60–75% of patients with soft-tissue ossification, heterotopic ossification of abdominal incisions are relatively rare and thus infrequently reported. This article details the manifestation of this relatively large heterotopic bone and provides a comprehensive review of the literature and pathogenesis of this unusual ossification. A review of the English literature from 1920 to the present produced only a handful of articles for a total of 185 reported cases. All had bone formed within vertical incisions, usually within 1 year of surgery, and 89% were males. Knowledge of this phenomenon and the variable size at presentation is useful to both the autopsy pathologist and the anthropologist in generating a diagnosis for abnormal calcifications.

KEYWORDS: forensic science, forensic anthropology, forensic pathology, heterotopic bone, myostitis ossificans, calcification, ectopic bone, osteogenic induction

Heterotopic ossifications are commonly referred to as myostitis ossificans (MO) and are associated with numerous conditions. They arise following a wide variety of "traumatic" (MO traumatica) or "neurogenic" (neurogenic MO) ailments, such as immobilizing injuries, surgical manipulations, severe burns, spinal cord injuries, central nervous disorders, closed head injuries, or cerebrovascular accidents. Alternatively, they may be genetic (MO progressiva) or "idiopathic" (MO circumscripta) in origin (1–3). By far, the most common heterotopic ossification is MO traumatica, which accounts for roughly 60–75% of patients with soft-tissue ossification and is frequently seen in patients with total hip arthroplasty (4). Up to 90% of these patients develop paraarticular ossification following surgery. MO traumatica also occurs in 30% of patients with severe burns or spinal injuries (5). In addition to these far more common presentations, heterotopic bone may also develop in abdominal surgical incision sites (5–9).

Heterotopic ossification of abdominal surgical incisions is a relatively rare finding and thus infrequently reported. However, knowledge of this variety may prove useful to both the autopsy pathologist and the anthropologist when abnormal calcifications are discovered at autopsy. Here, we present an unusual case involving a large calcification that was found during autopsy.

Case Report

A 72-year-old man was found dead in his home and was subsequently brought to the Office of the Medical Investigator in Albuquerque, New Mexico, for autopsy and identification. He was found to be a well-nourished adult weighing 198 lbs and measuring 71 inches in height. Based on autopsy results, the cause of death was determined to be hypertensive and arteriosclerotic cardiovascular disease, and the manner of death was classified as natural. A secondary finding, but unrelated to the cause of death, was cancer of the right lung. Additionally, a 30.5 × 5.1 cm vertically aligned calcified mass was found just deep to a 30.5 cm midline abdominal scar (Figs. 1 and 2). No additional soft-tissue calcifications were found.

The calcification was a secondary finding at autopsy and was not viewed as a factor contributing to the individual's death. However, as cancer of the left lung was also discovered, a differential diagnosis of this mass was warranted. The calcified mass extended from the xiphoid process and tapered toward the umbilical region, ending at a point just left of the umbilicus. It consisted of a peripheral rim of lamellar bone, which was round in cross section and surrounded a cartilaginous core. The bone contained multiple holes that were seemingly formed as new bone was laid down rapidly in a haphazard and erratic manner. Four conditions were considered in the differential diagnosis. These include (1) metastatic calcification, (2) dystrophic calcification, (3) idiopathic calcification, and (4) heterotopic ossification.

Soft-tissue ossifications are differentiated from amorphous calcifications by the presence of osteoblasts, trabeculation, or bone ordered upon a collagenous matrix. These are commonly referred to as MO, heterotopic ossifications, or ectopic ossifications and result from a variety of causes: trauma, tumors, neurological conditions, fibrodysplasia ossificans progressive, and a multitude of others (4,10,11).

In the current case, the mass was not only ordered upon a collagenous matrix but also presented lamellar bone and obvious osteoblastic activity. This eliminated amorphous (metastatic, dystrophic, or idiopathic) calcifications as potential diagnoses and consequently favored the current case as a heterotopic ossification.

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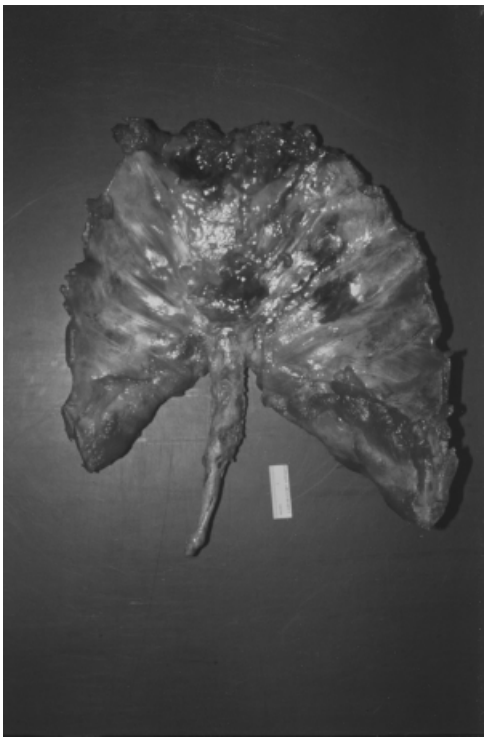

FIG. 1—*Posterior view of the thoracic plate showing the ossified mass extending from the xiphoid process inferiorly.*

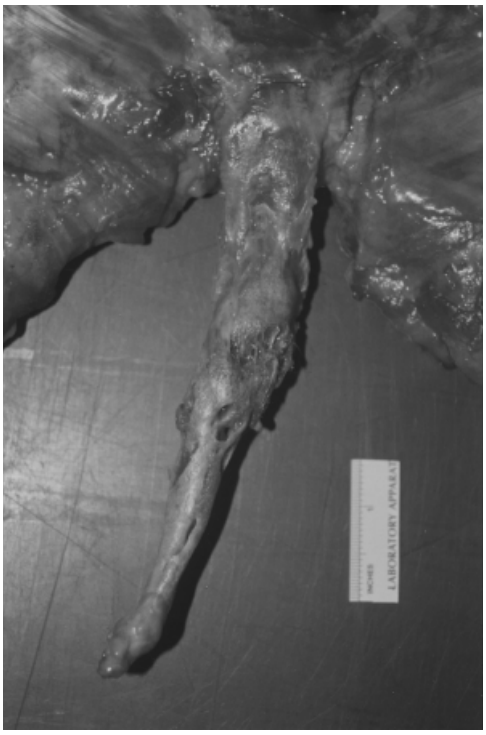

FIG. 2—*Posterior view of the thoracic plate showing the ossified mass extending from the xiphoid process inferiorly.*

The ossification lies just deep to, and follows the path of, an abdominal surgical incision scar. Thus, the ossified mass was diagnosed as a heterotopic ossification of an abdominal incision.

Discussion

Literature Review

A review of the English literature from 1920 to the present produced only a handful of articles on heterotopic bone formation in abdominal incisions for a total of 185 reported cases (see Table 1). While many of these reports contain little clinical detail, such as the length of heterotopic bone or the amount of time that elapsed since surgery to bone formation, it is clear that these ossified masses predominantly formed in males, along vertical incisions, and largely appeared within 1 year following surgery.

As observed in Table 1, 89% of the patients are male. The cause for the tendency of abdominal ossifications to occur in males, with a striking prevalence, is quite puzzling and at the present time remains elusive. One explanation, suggested by Charles and Hunt (12), is that vertical incisions are more frequent among males due to abdominal operations that are directed toward male dominated diseases. These mainly include diseases of the stomach, prostate, and bladder. Abdominal operations performed at a high frequency in women, on the other hand, include hysterectomies and cesarean sections, both of which are typically performed by a low transverse, rather than vertical incisions. Interestingly, all of the midline ossifications are vertically oriented and their formation appears to be restricted to vertical abdominal incisions, rather than transverse incisions. To date, there are no descriptions of heteroropic ossifications presenting in transverse incisions.

TABLE 1—*Reported cases of heterotopic ossification in abdominal incision wounds from 1920 to the present.*

Date	No. of Males/ Females	Time Elapsed	Bone Length (cm)	Age Range (years)	Age Mean (years)	References
1920–1929	6/0	21 d–25 m	2.5–6.4	25–70	43	(31–33)
1930–1939	4/1	1.5–16 m	3.8–12	51–80	63.4	(34–38)
1940–1949	1/0	1.5 m	5.2	54	54	(39)
1950–1959	9/0	2–37 m	7.6–15	34–71	54.1	(23,40)
1960–1969	29/3	14 d–14 y	1.0–15	30–78	56.7	(9,41–45)
1970–1979	47/9	24 d–4 y	3–15.5	25–81	55	(13,17,18,46–49)
1980–1989	36/5	14 d–30 y	1.6–23	22–78	52.4	(2,7,15,16,19,22,50–55)
1990–1999	30/1	11 d–48 m	0.7–14.5	18–81	52.1	(5,8,12,14,56,57)
2000–2005	3/1	5 m–7 y	2–12	37–76	53.5	(6,20,58,59)
Total	165/20	11 d–30 y	0.7–23	18–81	54	

d, days; m, months; y, years.

An alternative explanation, which has not yet been tested, proposes that males, having greater anteroposterior chest diameters, are predisposed to increasing abdominal tension following surgery. This abdominal tension is therefore proposed as a possible stimulus for heterotopic bone formation (12,13). While this would explain the marked male predominance of the condition, this theory is currently unsupported, untested, and largely remains a supposition.

Heterotopic ossification has been discovered as early as 11 days after surgery and as late as 30 postsurgical years (5,14,15). In the majority of patients ossification had formed between 4 and 6 months following surgery. The masses were typically discovered by the doctor at a postsurgical follow-up appointment, or when a patient complained of abdominal pain and/or discomfort. In some cases the abdominal heterotopic bone was small in size or patients were asymptomatic and the interval went undetected until a second operation was performed. Consequently, the incidence is probably much higher than is reported in the literature. In the current case, the time of postoperative ossification is unknown. The relatively large size of this bone was due to either the surgery occurring many years previously or resulted from the very large incision size (30.5 cm).

According to previous reports, the size of vertically oriented ossifications has a large range: 0.7 cm (14) to 23 cm (16). The current case presented with an ossified mass measuring 30.5 cm in length, the largest heterotopic bone in an abdominal incision to be reported. Review of the literature revealed no association between time after operation, incision length, and the ultimate size of the heterotopic bone. For example, Jacobs et al. (14) reported a case with a small ossification, 1 cm in length, which remained stable 3 years after surgery. A second case had a 3.7 cm bone that presented within 21 days after surgery and remained stable in length. Thus, as bone size did not appear to increase over time, size appears to be unrelated to postoperative intervals. Furthermore, they reported on two additional cases with heterotopic bones measuring 1.3 cm in size. The first case had an abdominal incision that was 0.7 cm in size, while the second patient underwent a surgical procedure requiring an 11.2 cm incision. In these cases, the abdominal incision size varied greatly but produced ossifications of the same size. As such, surgical incision size appears unrelated to heterotopic bone size. It seems more likely that heterotopic ossification size merely reflects idiosyncratic variation. Alternatively it is the result of multiple factors relating to the underlying pathogenesis of this condition.

Pathogenesis

The pathogenesis of bone formation in abdominal incisions is still unknown. Earlier studies proposed that vertical incisions at or near the xiphoid process or pubic symphysis liberated osteoprogenitor cells from the perichondrium or periosteum to "seed" the wound and create bone (9,13,17,18). This "seeding" theory, as pointed out by Gaffey and Winston (5) and Reardon et al. (8), has been largely abandoned as it fails to explain the reports of heterotopic bone formation in paramedian or pararectus incisions, where neither the xiphiod nor pubis are involved. Further, this theory neglects to address the low incidence of bone formation among women, or following trauma or surgical procedures where infusion of osteoprogenitor cells undoubtedly occurs. An alternative theory, that most investigators currently support, is that mesenchymal cells residing within the muscles are transformed into osteoblasts or chondroblasts in response to a stimulus. This process has been termed osteogenic induction (2,3,5,8,9,11,19,20)

Chalmers et al. (21) proposed three conditions necessary for osteogenic induction: (1) osteogenic precursor cells, (2) a permissive environment, and (3) a stimulus. Mesenchymal cells have the ability to generate cartilage, bone, and muscle, but cannot differentiate without stimulating agents. While the stimulus for heterotopic ossification is currently unknown, a number of possible agents have been proposed. These include abdominal suture tension and multiple humoral and/or hormonal factors.

As mentioned earlier, it has been suggested that suture line tension in males may provide the stimulus necessary for bone formation to occur within an abdominal incision (14). It is thought that males, having greater chest diameters and/or undergoing heavier manual labor, are more susceptible to tension at the site of surgical incision, thus promoting bone formation (12,13,22,23). While it is quite possible that increased abdominal tension may influence the formation of bone within this area, it largely remains a hypothesis that has not yet been tested. However, it is highly unlikely that all male patients have larger chest diamters or labor more than women, since many of the patients presenting with heterotopic bones are older than 60 or 70 years in age. Further, Orava et al. (22) reports on seven cases where heterotopic bone developed in upper midline abdominal scars. Of these cases, five were documented as having "strenuous occupations." However, all of these patients had developed the calcifications during a postoperative period where the patients were relatively inactive and had not yet returned to work. Thus, this theory remains inadequate.

Alternatively, humoral and hormonal factors are believed to stimulate chondrogenesis and osteogenesis at the site of incision, and bone morphogenetic proteins (BMPs) are believed to comprise a major component of this process. BMPs influence the proliferation and differentiation of mesenchymal cells, cartilage formation, vascular invasion, and osteogenesis during growth (10). In a study by Urist et al. (24) it was shown that extracted proteins from a bone matrix, cultured in muscle tissue, can invoke cartilage or ectopic bone formation. Thus, it was concluded that in the correct local environment, BMPs are most probably the stimulating agents responsible for heterotopic bone formation. Similarly, Kishitmoto et al. (25) found that BMPs were the facilitating agents in ectopic woven bone formation within mouse skeletal muscle tissue. At the present time, BMPs are probably the best factors implicated for stimulating heterotopic ossification.

To a lesser extent, many other stimulating factors have been implicated, such as interleukin-1β (26), prostaglandin E_2 (27), growth hormones (10,28,29), insulin-like growth factors, and fibroblast growth factors (28–30). While all of these agents have been associated with enhanced osteogenesis, none has been shown to stimulate heterotopic bone formation autonomously. Instead, it is possible that some or all of these, acting together, provide the stimulus necessary for heterotopic bone to form. It is very likely that heterotopic ossification is multifactorial in origin; activated by a variety of humoral and hormonal stimuli, triggering mesenchymal cells to differentiate.

Conclusion

The autopsy of a 72-year-old white male revealed a 30.5×5.1 cm vertically aligned heterotopic ossification just deep to a prior abdominal surgical incision. This relatively rare type of

ossification was similar to those previously reported, although much larger. Heterotopic ossification of abdominal incisions predominantly affects males, is exclusively restricted to vertical incisions, usually presents within 1 year of surgery, and varies greatly in size. The size of the ossification is probably the result of idiosyncratic variation, rather than incision size or time since surgery, and most likely arises via osteogenic induction from multiple stimulating factors. Familiarity with the morphology and occurrence of heterotopic ossifications will help the autopsy pathologist and the anthropologist in the differential diagnoses of abnormal calcifications or help to identify an unknown individual presenting with an abdominal ossification.

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