1 **TITLE:** Extensive periosteal new bone formation in a skeleton from post-Medieval
2 Chichester, England: A probable case of metastatic prostatic carcinoma

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18 **Abstract:**

19 An elderly male skeleton from a site in Chichester, UK, was found with a widespread
20 periosteal reaction, principally affecting the axial skeleton and the pelvis. Radiography
21 showed the presence of sclerosing infiltrates, mainly involving the lumbar vertebrae and
22 pelvis. The differential diagnosis is discussed, reaching the conclusion that hypertrophic
23 osteo-arthopathy (HOA) is the only reasonable alternative condition likely to produce such a
24 widespread periosteal reaction as found here. HOA does not produce secondary deposits in
25 the skeleton, however, and we conclude that his is most likely a case of prostatic carcinoma.

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1. INTRODUCTION

According to the World Health Organisation (WHO), cancer ranks globally as one of the primary causes of mortality and morbidity, with numbers of new cases expected to rise by as much as 70% over the next two decades (WHO, 2015). This reflects the popular notion that cancer, considering all the various types, is common. It is now well-known that cancer is a disease of great antiquity, with evidence stretching back as far as 1.5 million years (Capasso, 2005). Cancer of the prostate, in particular, is a common condition accounting (in the UK) for approximately 45,000 cases annually, while in the United States it is estimated that there are more than 1.2 million new cases per year (Hage et al., 2000). Its occurrence is strongly positively correlated with age, the incidence being greatest in men aged 75 – 79 (ca 900 cases/10^5)(Cancer Research UK, 2017). There has been a considerable increase in the number of cases in the last fifty years or so, largely due to the increasing age of the population. The disease is not new, and there is no evidence that the age-specific incidence would be any different to today, although the absolute number of cases would have been much smaller due to a generally lower expectation of life.

The disease shows a great propensity to spread to bone (Soloway et al., 1988), especially the pelvis and lower vertebrae, and generally forms sclerotic lesions within bone although lytic lesions are not unknown (Bubendorf et al., 2000). The lesions are most often confined to the interior of the bone and do not cause any alteration in shape, making diagnosis of this disease difficult in human remains. Cases with sclerosing metastases have been reported in the skeleton (Schultz et al., 2007; Tkocz and Bierring, 1984; Wakely et al., 1995), in cremated remains (Grévin et al., 1997), and in a mummy (Prates et al., 2011). There is a much rarer form of the disease which is characterised by the production of widespread, often spiculated, periosteal new bone (Bloom et al., 1987; Reigman and Stokkel, 2004; Vilar, et al., 1979) and it is this type that is most easily recognised in the skeleton (Anderson et al., 1992; Ortner et al., 1991; Waldron, 1997), simply because the lesions are so obvious on direct examination. The periosteal lesions can be reproduced in mice following the injection of prostate cancer cells directly into bone, but their pathogenesis is presently not clear (Henry et al., 2005; McCabe et al., 2008).

Of all the possible neoplastic diseases that can impact the skeleton (breast cancer, lung cancer, plasmacytoma, multiple myeloma, etc.), prostate cancer is one of the most commonly observed in archaeology, with over 15 cases reported throughout the literature (Anderson et al., 1992; Baraybar and Shimada, 1993; de la Rúa et al., 1995; Grévin et al., 1997; Klaus, 2017; Lieverse et al., 2014; Luna et al., 2015; Mays et al., 1996; Merczi et al., 2014; Molnár et al., 2009; Prates et al., 2011; Schlott et al., 2007; Schultz et al., 2007; Tkocz and Bierring, 1984; Wakely et al., 1995; Waldron, 1997; see

68   Ghabili et al., 2016 for a review of the current palaeopathological literature on prostate cancer). We

69   present here a case of a skeleton with wide spread periosteal new bone (or PNB), together with

70   radiological evidence of sclerotic secondary deposits, which we suggest represents a case of

71   prostatic cancer dating to the 18th/19th centuries.

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73   **2. MATERIAL AND METHODS**

74   2.1 *The skeleton*

75   The skeleton under investigation here (designated SK.2788) was uncovered as part of an

76   archaeological rescue excavation of the disused cemetery St Michaels Litten in Chichester, England.

77   Interred in a coffin, SK.2788 dates to the latter part of the cemetery's occupation (the 18th and 19th

78   centuries).

79   A biological profile of the remains was performed by the authors using standard anthroposcopic and

80   metric methods (Buikstra and Ubelaker, 1994). Due to the somewhat fragmentary nature of the

81   remains (especially in the pelvic region) and the extensive amount of post-mortem taphonomic

82   modification, sex estimation was based primarily on the metric assessment of the femoral head

83   (Bass, 1995), and age assessment was based on the marked degree of tooth wear (Brothwell, 1981)

84   and the small portion of the auricular surface present (Lovejoy et al., 1985). Considering these

85   factors, it was concluded that the skeleton was likely male and of an advanced age [over 50 years].

86   Furthermore, the individual was robust, with marked muscle attachments across all bones; this high

87   level of bone forming across the skeleton may account for the very pronounced degree of

88   pathological changes observed (refer to Section 3).

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90   2.2 *Methods*

91   The primary evaluative framework for understanding the nature of the observed pathological

92   changes was comprehensive macroscopic analysis of the entire skeleton coupled with radiographic

93   imaging of specific skeletal elements known to be of diagnostic value in cases of possible neoplastic

94   disease. Following descriptive analysis, a thorough differential diagnosis was undertaken, from

95   which a presumptive diagnosis was made. No further exploratory methods were attempted, such as

96   CT or basic histology (see De Boer et al., 2013), as there would be no grounds for comparison with

97   the known clinical features. However, new approaches, such as proteomics (Schlott et al., 2007;

98   current review on the state of molecular palaeopathology see Nerlich 2017) are proving extremely

99   promising and will likely expand our knowledge of cancer in the past, with more and better

100   diagnoses.

101

102   **3. RESULTS**

103   3.1 Description of the skeleton and the bony lesions

104   *Preservation and general appearance*

105   The skeleton is largely complete, although fragmentary in places. Only a few of the vertebrae have

106   survived, the pelvis is highly fragmented and fragile, and the ribs are in poor condition. Those

107   elements that are present are in good condition, with sound external cortical bone, where not

108   affected by disease. The cranium and mandible are in fair condition, with some fragmentation and

109   post-mortem damage. All long bones are present and, while broken in places, still retain most

110   diagnostic regions and are largely measureable. Further, all long bones present with well-marked

111   muscle attachments and marked osteophytic growth that appears normal.

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113   *The skull*

114   Both blastic and lytic lesions are present across the skull. Lytic lesions are confined to the internal

115   surface of the cranial vault (Fig 1c), the backs of the orbits, and the base of the cranium; only those

116   in the orbits and right temporal (inferior surface) are penetrative (Fig 1a). The vault and base of the

117   cranium are also somewhat thickened, with marked expansion of trabecular bone in the basilar

118   occipital and inferior temporal regions. There are small plaques of PNB along the right temporal, and

119   right/left mandibular rami (Fig 1b). Some mixed changes are also visible along the inferior surface of

120   the right greater wing of the sphenoid.

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122   **[INSERT FIGURE 1 HERE]**

123

124   *Appendicular skeleton*

125   The proximal portion of the right and left humeri present with marked PNB (Fig 2c), with a very

126   porous and swollen appearance; in cross-section, the humeral shafts show marked expansion of

127   trabecular bone, with a much reduced medullary cavity retained. The distal ends of both humeri are

128   un-affected and appear normal externally. No observed changes were observed on the left radius

129   and ulna. The right ulna has notable PNB along the distal/latero-posterior portion of the shaft, as

130   does the right radius.

131   Similarly, the right and left femora exhibit marked PNB across the proximal half of the shaft, mostly

132   concentrated around the base of the femoral neck. A large swelling is present along the lesser

133   trochanter (and just inferior) on the right femur; this mass of PNB extends more than 5mm from the

134   natural shaft of the femur and has a bulbous, undulating appearance. A similar lesion is present on

135   the left tibia (Fig 2d), along the lateral/posterior surface of the proximal end. Both tibiae further

136   present with PNB plaques along the entire length of the shaft (Fig 5b). The fibulae both appear

137   mostly unaffected, with just a few areas of isolated PNB across the shafts. As with the upper limbs,

138   the femora and tibiae, in cross-section, both show a massively expanded internal structure, with

139   virtually no room for a marrow cavity; this can be seen clearly in the radiographs (Fig 5).

140   There is no evidence of new bone growth or any periosteal changes in the hands or feet.

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142   **[INSERT FIGURE 2 HERE]**

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144   **[INSERT FIGURE 3 HERE]**

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146   *Axial Skeleton*

147   Of all the bones in this specimen, it is those in the axial skeleton that present with the most dramatic

148   changes. The vertebrae (particularly those from the lower thoracic and lumbar regions) are thick and

149   solid. The os coxae, both sides, are completely transformed; the bone is thick and spongy, with no

150   clear definition between external cortical bone and internal trabecular bone (Fig 2a). The external

151   surfaces of both os coxae are further covered with extensive PNB and large osteophytic growth (Fig

152   2b); both appear highly vascular and swollen, with the only normal areas being those in/around the

153   acetabulum.

154   The scapulae and clavicles are also show a number of marked changes, particularly in the extensive

155   and large bone growths along the medial border/posterior surface of the scapulae. These growths

156   cover nearly the entire medial border of both scapulae and the regions inferior/superior to the spine

157   of the scapulae. The growths here extend further than 5mm from the surface of the scapulae; a

158   microscopic view of the border between the normal bone and this marked abnormal growth can be

159   seen in Figure 3. In a similar fashion to the long bones, the clavicles are covered in PNB, and appear

160   porous and thickened; in cross-section, no obvious medullary cavity is present, as the internal

161   surface is swollen and filled in with new bone. A diagram of the extent and location of all PNB

162   reactions across the skeleton can be seen in Figure 4.

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164   **[INSERT FIGURE 4 HERE]**

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166   3.2 Radiography

167   Radiography of various skeletal elements showed the presence of periosteal new bone on the long

168   bones some of which was contiguous with the cortex and some separated from it (Fig 5b). The

169   lumbar and thoracic vertebrae all showed the presence of sclerosing infiltrates (Fig 5c) as did the

170   fragments of the pelvis (Fig 5a).

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172   **[INSERT FIGURE 5 HERE]**

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174   **4. DISCUSSION**

175   The features observed in SK 2788 – the marked and extensive periosteal new bone growth; the

176   heavy, thickened bone; the loss of the medullary cavity in the long bones; the lytic lesions in the

177   cranium; and the notable sclerosis in the radiographs – all point to a systemic condition that caused

178   bony changes to nearly the entire skeleton. From first glance, neoplastic disease seems a likely

179   culprit, as number of cancers have the potential to progress from their primary site and metastasise

180   to bone. However, cancers are relatively rare in the palaeopathological literature, so one must use

181   caution when coming to this as a potential diagnosis. A number of primary tumours have a

182   predilection to spread to bone, but four primary sources, breast, lung, plasma (myeloma) and

183   prostate, account for at least three quarters of all bony metastases (Coleman, 2001; Hage et al.,

184   2000; Roodman, 2004). Other primary sites that are less often observed include the kidney, thyroid,

185   and skin (Coleman, 1994; Coleman, 2001).

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187   Primary cancers will metastasise with their own pattern in bone, with either predominantly sclerotic

188   (blastic) or lytic lesions; Figure 6 shows the increasing/decreasing likelihood depending on the

189   condition. A primary breast tumour can easily be ruled out in this present case since the skeleton is

190   that of a male, for although breast cancer does arise in males, it is extremely rare with an incidence

191   (in the UK) of about one case in every hundred thousand men (Cancer Research UK, 2017). Prostate

192   cancer, on the other hand, is almost a thousand times more common. A primary lung tumour can

193   also be ruled out with some confidence, lytic lesions being far more common than blastic. In

194   Skeleton 2788, the lesions are almost entirely blastic/sclerotic, save the lytic lesions in the cranium,

195   which supports the potential diagnosis of primary carcinoma of the prostate.

196

197   **[INSERT FIGURE 6 HERE]**

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199   A prominent periosteal reaction is typical of primary bone tumours such as osteosarcoma or Ewing's

200   sarcoma but it is a rare concomitant of bony metastases. Where it does occur it seems to be most

201   commonly associated with carcinoma of the prostate although it has also been found with tumours

202   of the breast, lung, and intestinal tract, among others (Rosenthal, 1997). It is readily differentiated

203   from the periosteal new bone found in primary bone tumours by clinical and radiological features,

204   and by the age of onset; primary bone tumours occurring at a much younger age than secondary

205   ones (Bloom et al., 1987).

206

207   The question now arises as to which other conditions might be confused with the periosteal reaction

208   produced in prostatic cancer. There are several that may produce a localised periosteal reaction in

209   adults, rather fewer that produce a generalised or widespread reaction (Table 1). Thyroid acropachy

210   is extremely rare and, as its name suggests, produces new bone predominantly on the tubular bones

211   of the hands and the feet. In leukaemia the axial skeleton is mainly affected and the disease is rare.

212   Fluorosis is primarily a disease of the entheses, which leaves hypertrophic osteoarthropathy (HOA)

213   as the only realistic alternative diagnosis.

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220   Table 1. Causes of Periosteal Reactions in Adults.

Type of periosteal reaction	
Localised	*Generalised*
Psoriatic arthropathy	Primary and secondary hypertrophic osteoarthropathy (HOA)
Reactive arthropathy	Thyroid acropachy
Fractures and other trauma	Leukaemia
Primary bone tumours	Fluorosis
Infections	
Venous stasis	
Burns	

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223   Primary HOA is an extremely rare genetic condition, unlikely to be encountered in the skeleton since

224   only a few hundred cases have ever been reported. Secondary HOA is much more common although

225   its prevalence is not known. It occurs in animals and in man (Pineda and Martinez-Lavin, 2013;

226   Thorsson, 2015), and in both it is mainly encountered in the context of pulmonary disease, or other

227   diseases in which the pulmonary circulation is compromised. The periosteal reaction seems to be

228   secondary to clubbing of the fingers in the living, and is symmetrical, principally affecting the

229   proximal and distal ends of the long bones. In HOA there would be no infiltration of sclerosing

230   metastases but there could conceivably be lytic lesions present if a primary lung carcinoma were the

231   underlying cause. Overall, the combination of a widespread periosteal reaction in Skeleton 2788,

232   with or without sunbursts, with sclerotic secondaries in the bone (especially in the axial skeleton)

233   should be sufficient to make the likely diagnosis of prostatic cancer. The important of radiography in

234   arriving at the diagnosis cannot be over-emphasised, however.

235

236   Case reports of cancer in the past are important in that they clearly demonstrate that the disease is

237   of ancient lineage and not a modern disease as some clinicians are apt to suppose (Capasso, 2005;

238   Nerlich et al., 2006). They cannot, of course, give any indication of the frequency of malignant

239   disease in the past, or of any fluctuations that may have occurred; for this a well conducted series of

240   prevalence studies would be needed. What is certain is that the prevalence of malignant disease is

241   under-estimated in skeletal assemblages. This is particularly true with prostatic cancer since, in the

242 absence of periosteal new bone, there are no morphological changes to suggest that the disease is

243 present. In general, affected bones may appear to be heavier than normal, and more cases would be

244 discovered if the skeletons of older male skeletons were routinely x-rayed when sclerotic

245 infiltrations might be discovered (Rothschild and Rothschild, 1995) although there may be difficulty

246 in differentiating prostatic secondaries from osteosarcoma or Paget's disease (Igou et al., 1995).

247 A number of reasons could be proposed for the dearth of archaeological evidence of cancer in

248 human remains, and there is likely no single explanation, but rather a combination of causative

249 agents. The simplest, and most obvious of these, is the fact that the vast majority of neoplastic

250 disease fail to create any bony changes. Most cancers originate in the organs of the body, with only a

251 few originating in the musculoskeletal system or metastasizing to it. For those that do affect the

252 skeleton, there can be profound changes to the structure and appearance of bone, which can then

253 secondarily be acted upon taphonomically. Already weak/altered bone is inherently more prone to

254 further destruction and alteration via the burial environment; this can lead to either complete loss of

255 areas of neoplastic change (or the whole skeleton) or to destruction of cortical bone such that any

256 changes are may no longer be present. Taphonomic alteration to bone is already a problem

257 archaeologically, and this can compound the problem of identifying possible neoplasms.

258 Another factor is the issue of identification itself. In clinical practice, the manner in which cancer is

259 diagnosed relies on methods not available to the palaeopathologist, and as such cannot always be

260 directly translated to the changes we can observe directly on bone. This makes clinical comparison

261 difficult, if not impossible. Confounding this is that the presentation of cancer in the skeleton can

262 mimic many other conditions, further challenging diagnosis.

263

264 **5. CONCLUSION**

265 Here, we have described and discussed an individual presenting with marked and extensive

266 periosteal new bone, which we believe represents a case of advanced metastatic prostatic

267 carcinoma. Considering the suite of observed skeletal changes, other primary cancer origin sites are

268 unlikely, with the only other possible diagnosis being HOA, albeit unlikely as well. Within the already

269 small number of cases of cancer reported across the palaeopathological literature, prostate cancer is

270 relatively well described, and as such, this new case provides only one more data point. Isolated case

271 studies of the various types of malignant disease are like signposts on the way, indicating as they do,

272 various stages in their history, but they cannot provide any information on what is of considerably

273 more interest, and that is, what the prevalence of cancer was in the past, its characteristics, and how

274 it might have altered over time. However, we must remember that it is vital to continue to report all

275 observed cases; the more we report, the clearer the picture of cancer in the past becomes.

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FIGURE 1. Blastic and lytic lesions observed in the skull. A) Penetrative defect through the left temporal bone (within the mandibular fossa); B) Plaques of periosteal new bone along the internal surface of the right mandible, with an observed expansion and alteration of the internal trabecular bone; C) Lytic, non-penetrative lesion along the internal surface of the vault, on the frontal bone.
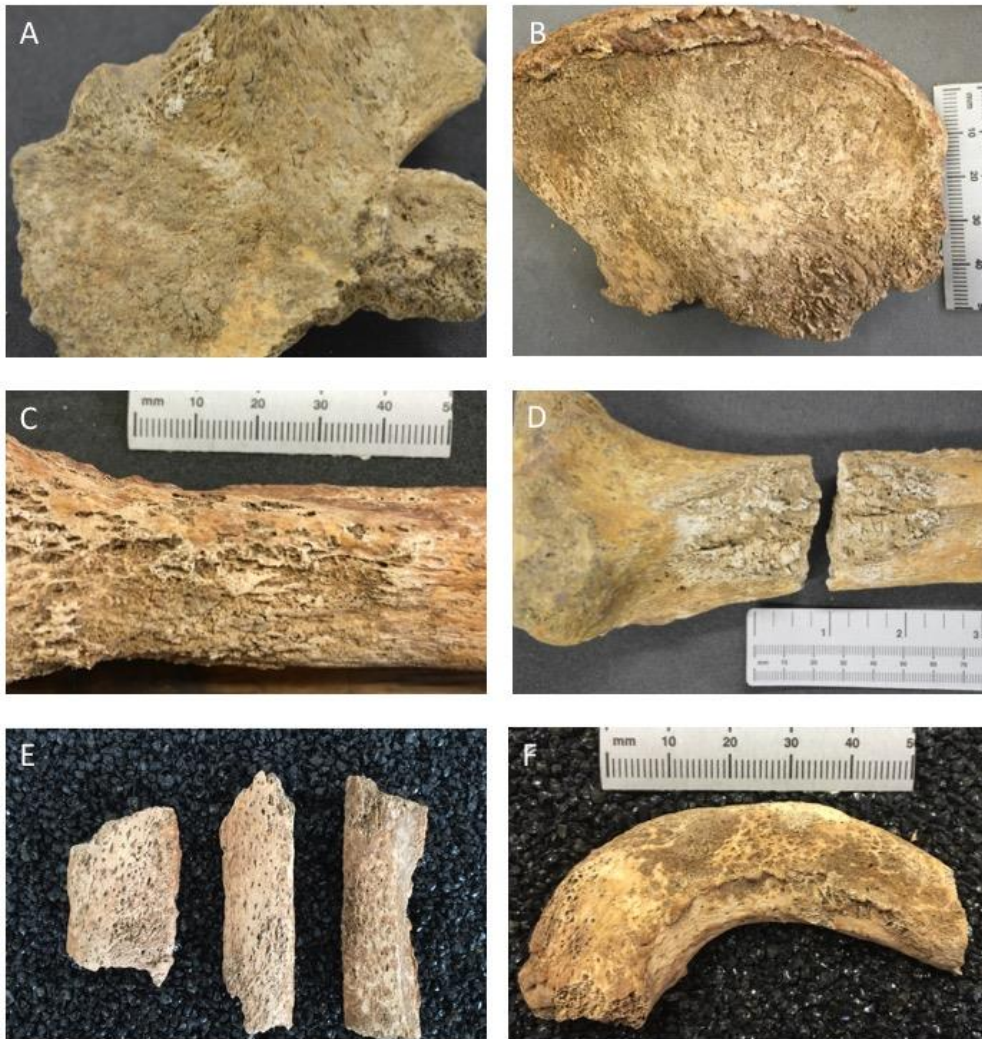
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FIGURE 2. Periosteal new bone growth across the appendicular and axial skeleton. A) Close-up view of the left os coxa; B) left Iliac blade; C) left proximal humerus; D) left proximal tibia; E) fragments of ribs; and F) right clavicle, acromial end.
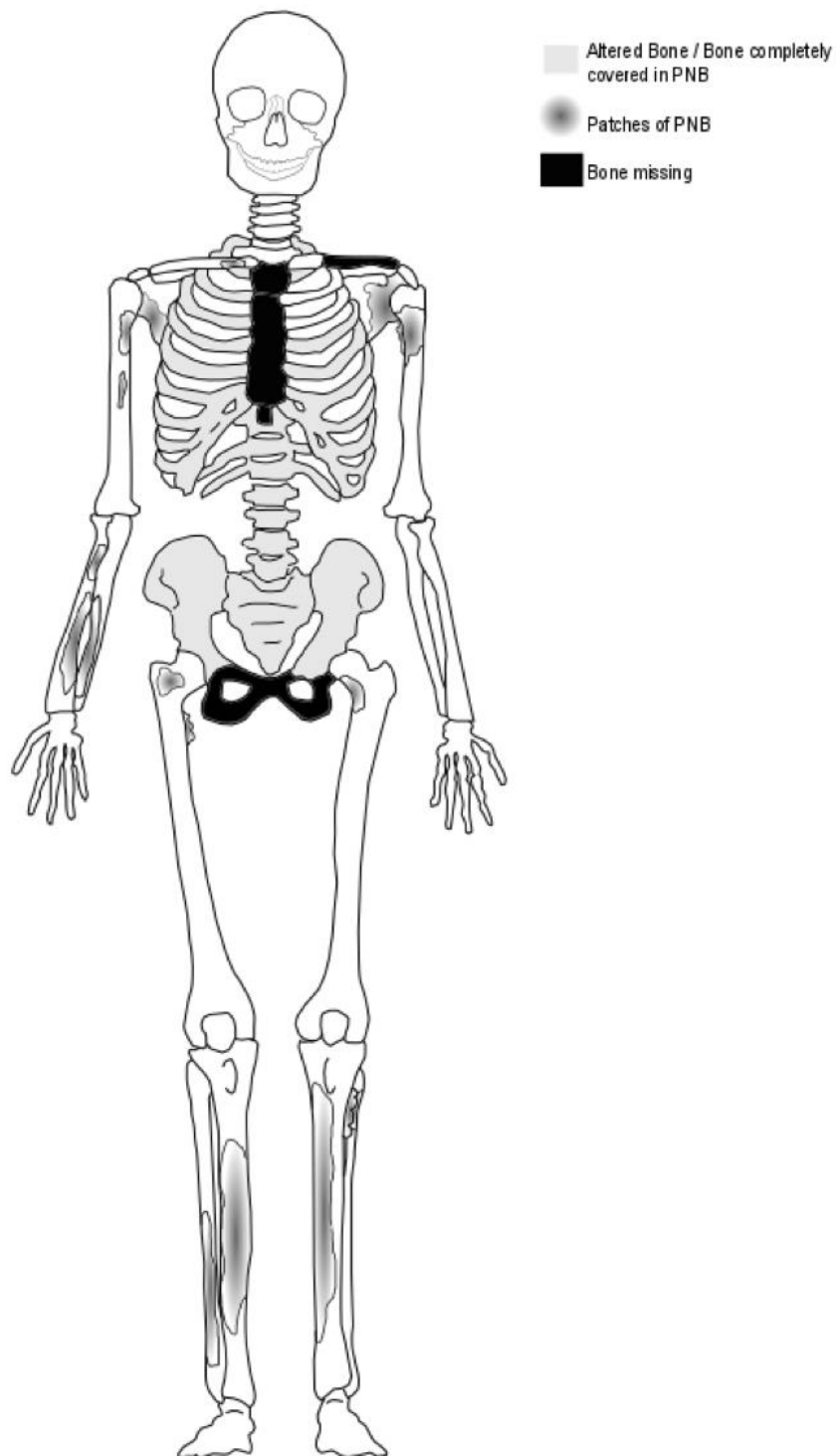
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FIGURE 3. Extensive periosteal new bone growth along the spine of the right scapula. The call-out
image is 20x magnification of the region along the growth zone for the new bone, showing a clear
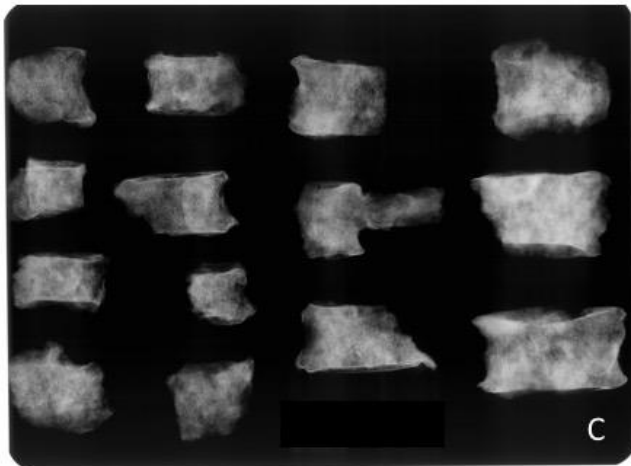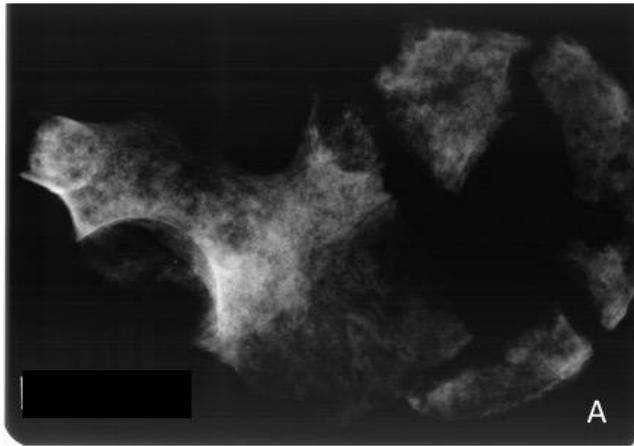distinction in the progression between normal and abnormal bone appearance.

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FIGURE 4. Diagram of the location and extent of PNB changes to Sk. 2788. The cranial changes are not included in this diagram, as the majority of changes are confined to the internal bony surfaces; please refer to Figure 1.

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FIGURE 5. A) X-ray of left pelvis fragments all showing areas of sclerosis, especially in the ilium around the sciatic notch; B) X-ray of both tibiae showing the presence of periosteal new bone on the shaft. Some of this new bone is contiguous with the cortex and some is separated from it; C) X-ray of fourteen thoracic and lumbar vertebrae, or vertebral fragments, all of which contain areas of sclerosis.

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FIGURE 6. Likelihood of developing lytic or blastic lesions in various types of metastatic disease that affect bone. Here, we can see that prostate cancer should present with mostly blastic/sclerotic lesions. Figure redrawn from Coleman, 2001.

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