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Metastatic bone disease: a review of various concepts and report of a case

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Skeletal metastatic disease is usually a disastrous cause of musculoskeletal pain. Although much has been learned concerning metastatic disease, patients presenting with skeletal pain or neuropathy and a history of carcinoma should be regarded with great suspicion. An overview, and study of one such case is discussed. (JCCA 1988; 32(3): 127–132)

KEY WORDS: metastatic disease, back pain, tumors, chiropractic.

L'affection métastatique osseuse est une cause désastreuse de douleur musculo squelettique. Bien que l'on ai beaucoup appris au sujet de l'affection mátastatique, les patients souffrant de douleur squelettique ou de neuropathie et avec des antécédents de carcinome doivent être considérés avec grande suspicion. Un aperçu et une étude d'un tel cas sont discutés. (JCCA 1988; 32(3):127–132)

MOTS CLÉS: Affection métastatique, douleur dorsale, tumeurs, chiropractie.

Introduction

Metastatic disease is the most frequent form of malignant neoplasm arising within the skeleton. Most metastatic lesions are derived from primary carcinomas, however, certain primary osseous sarcomas and melanomas may rarely metastasize to bone[1,2]. It has been estimated that approximately 70 percent of all primary malignant tumors have a metastatic potential while only approximately 30 percent remain primary. Tumors which have a propensity to remain primary are those which originate in the C.N.S. and basal cell carcinomas. Every other primary malignant tumor has a potential to metastasize[2].

The true incidence of skeletal involvement is difficult to assess, since statistics vary widely throughout the literature. Statistics based upon autopsy data conflict while figures evaluating the incidence of patients with evidence of skeletal metastasis vary from as low as 25–30 percent to as high as 85 percent[2,3,4,5,6]. Extremely high incidences may be a result of autopsy samples being primarily extracted from tumors which have an extreme propensity for osseous metastasis, the so-called "bone seeking" tumors. This disparity may also be influenced by the duration or stage of the disease which was sampled.[3] The most common sites involved with metastatic disease are the lungs, liver and skeleton in that order. Within the skeleton, the vertebral column, ribs, pelvis, proximal humerus, femora, sternum and calvarium are involved in a decreasing order of frequency.[1]

Pathophysiology

It is generally agreed that tumors originating from the prostate, breast, lung, kidney and gastrointestinal tract (colon), are implicated in approximately 80 percent of all skeletal metastasis[2,7,8]. In females, carcinoma of the breast may be responsible for 70 percent of all cases of skeletal metastasis, the remainder being attributable to primaries localized within the lung, thyroid, kidney and uterus. In males, carcinoma of the prostate produces 60 percent of metastasis, however, carcinoma of the lung contributes to an additional 25 percent of cases with skeletal metastatic disease[2]. Some tumors possess a distinct tendency to metastasize to the skeleton. Such tumors originate in the bronchus, breast, prostate and kidney[9,10]. Other tumors, including those originating in the sigmoid colon, pancreas, cervix and stomach infrequently exhibit skeletal metastasis[5,10,11].

Primary tumors may metastasize to bone by three distinct pathways; direct extension, lymphatic spread and hematogenous dissemination. Direct extension may particularly occur if the primary tumor is situated adjacent to an osseous surface. Tumors originating in the pelvic cavity, such as those of the uterus or colon may develop a direct communication with bones of the pelvis or sacrum. Tumors may also be seeded locally following surgical excision[2]. The role of lymphatic spread relative to tumorous emboli is yet vague. Some authors suggest that this mechanism may not exist due to the absence of lymphatic channels within bone[2]. However, other reports dispute this claim[1,5]. Tumors may extend to adjacent osseous structures secondary to erosion by hypertrophied lymph nodes. Normally, osseous extension via the lymphatic route will occur through the venous system[3,12].

The most common pathway for tumor emboli to secure access to skeletal structures is that of hematogenous dissemination, particularly through venous networks. This route accounts for the almost exclusive involvement of the axial skeleton since it contains the greatest percentage of hematopoietic tissue. The hematogenous spread of metastasis may also account for the tumor microemboli affecting multiple skeletal foci in addition to sites within the hepatic and pulmonary parenchyma[2,5,9,10,12]. Single sites of metastatic distribution account for approximately 10 percent of all skeletal metastatic lesions[2]. Although it is common to find tumor emboli within the systemic circulation of patients with primary disease, few retain the capacity for establishing an autonomous metastatic focus.

Primary tumors are composed of heterogeneous populations of cells containing sub-cell types which differ from the cells of the tumor of origin. Recently, further analysis has suggested that significant histological dissimilarities exist between metastatic lesions and the primary neoplasm from which they were derived. Only selected populations of cells contained within the

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primary tumor may have the potential to metastasize[12]. Various factors influence the ability of neoplastic microemboli to become established metastatic tumors. Certain malignant cells lack contact inhibition and cohesiveness which permit cells to traverse localized tissue barriers by the release of degradative enzymes. Vascular invasion occurs via penetrance into an efferent lymphatic or vascular channel. Most tumor cells exit the primary site via lymphatic channels and capillary veins. Tumor cells may traverse vascular walls via diapedesis or proteolytic destruction. These mechanisms also occur at the site of metastasis[12]. The rich network of venous sinusoids contained within the "red marrow" of the axial skeleton permits increased perfusion ratios and direct communication with trabecular bone. Direct reflux through the valveless Batson's paravertebral venous plexus augmented by muscular contraction and increased intrabdominal pressure collectively increases the vulnerability of the "red marrow" within the axial skeleton to the metastatic phenomenon. Once within bone, tumor cells spread through the medullary cavity by way of the Volkmann and Haversian canal systems[1,3,10].

Additional factors influencing metastatic dissemination include vascular transport and endothelial attachment of tumor emboli. It has been estimated that fewer than 0.1 percent of circulating tumor emboli survive. Circulating tumor emboli may be protected by a fibrin-platelet clot which provides an environment for division and a method of adherence to capillary endothelium. A colony of metastatic cells within a host organ can not generate a significant metastatic focus until separate vascularization is acquired. Without an adequate vascular supply, tumor cells become dormant, but remain viable. Therefore, the sequential completion of many factors is required for the successful production of a viable metastatic macrometastasis which may continue to thrive within a host organ. In the case of macrometastases within osseous tissue, several responses to the thriving neoplasm can be anticipated[1,3].

Radiographically, the pattern produced by osseous metastatic invasion is one of a simultaneous and continuous process of bone destruction and reformation. If the process of destruction predominates, the lesion appears osteolytic. Conversely, if bone formation predominates, the lesion will assume an osteoblastic appearance. When bone formation is equivalent to bone destruction, mixed osteolytic-osteoblastic lesions are the rule.[13] Osteoblastic lesions arise whenever there is a propensity for the primary tumor to possess a fibrous stroma. This stroma serves as a matrix for intramembranous bone formation in the presence of osteoprogenator cells. Only tumors, such as those of prostatic origin contain this kind of fibrous stroma and are thus associated with this type of bone formation[13]. Humoral products liberated by neoplastic cells, may stimulate osteoid production from osteoblasts and have also been associated with bone production[13,5]. Reactive new bone formation, produced in an attempt to repair destroyed or stressed trabeculae, may also give rise to osteoblastic lesion development[2,5,13].

Osteolysis conversely is mediated by the elaboration of osteoclast stimulating factors by tumor cells[5,13]. This mechanism has however been disputed by various authors.[2] It is however, generally conceded that lytic metastatic defects are produced by the mechanical effect of tumor growth resulting in selective resorption of medullary bone[2,5,13].

Imaging

Conventional radiography remains the most common method of evaluating skeletal metastasis. Analysis of plain film radiographs requires that no less than a 30 percent bone loss be present before detection is possible. Although other imaging modalities are more sensitive, a plain film examination of the axial skeleton fails to reveal metastatic lesions in only 9 percent of patients within known metastatic disease[7]. The reliable identification of metastatic lesions on plain films generally depends upon the site of involvement, the degree of osseous destruction and the integrity of the overlying cortex.

Most metastatic lesions are osteolytic (75 percent). They arise within the medullary cavity of bones of the axial skeleton in 80 percent of all affected patients[2]. Eccentric cortical metastases are rare, but have been associated with bronchogenic carcinoma[5,14]. Primary tumors associated with osteolytic metastases are those from the lung, breast, kidney, thyroid and gastrointestinal tract. In children, neuroblastoma is a frequent etiology underlying osteolytic disease.

There are several patterns of osseous destruction associated with lytic metastatic disease. Diffuse lesions dispersed throughout the spine and pelvis is the pattern which usually prevails. If such a distribution is disclosed in a female, metastatic carcinoma from the breast or lung should be favoured[4]. This pattern can produce focal or diffuse pathological vertebral body fractures in the lumbar, thoracic and cervical spines in a decreasing order of incidence. Spinal involvement is the most common and harbours 40 percent of all skeletal metastatic defects. Changes in density, trabecular architecture and vertebral contour provide clues to the presence of metastatic foci. Loss of one or both pedicles, Schmorl's nodal formation, and vertebra plana are features commonly attributed to metastatic disease. The disc spaces are typically preserved[1,3,15,16,17].

In flat bones, multiple, ill-defined lytic lesions of varying size may be apparent. The lesions may coalesce to form a "motheaten" or "permeative" lytic pattern. Focal, expansile, "blown-out" lesions may be associated with metastasis from the kidney or thyroid, and are more likely to assume a "geographic" appearance[4,11]. Focal rib expansion or destruction secondary to metastatic involvement may produce the classic "extrapleural sign". A soft tissue mass is an uncommon radiographic sign of skeletal metastasis but may be reliably associated with rib lesions when they occur[2]. Lytic metastatic disease may also affect the proximal humerus and femur. The metaphyseal or diaphyseal regions are usually favoured and the permeative, medullary pattern with cortical destruction and pathological fracture may be evident. Joint spaces are normally spared[2].

Metastasis occurring distal to the elbow and knee are unusual,

but may be present in the feet and hands in the form of osteolysis of a distal phalanx. Tumors of the lung, breast and kidney may, upon occasion, produce this pattern if the extent of dissemination becomes widespread[2,11]. Periosteal reactions to metastases are rare and are more likely a response to underlying pathological fracture than to the tumor[11]. Tumors arising from the prostate and neuroblastomas however, may produce a classical "sunburst" periosteal reaction[2,11,18].

Osteoblastic metastasis is generally featured by focal or diffuse increases in osseous density. This apearance accounts for approximately 15 percent of all skeletal metastasis[2]. Osteoblastic metastatic disease usually produces a pattern of multiple, discrete lesions, or a diffuse, ill-defined, "snowball" pattern[4,2]. Tumors associated with this variety of metastasis are those which originate in the prostate in males, and the breast especially following radiotherapy, in females. Other tumors related to blastic change are those which originate in the bladder, stomach, lung (particularly small-cell and adenocarcinomas), carcinoma of the gastrointestinal tract, and osteosarcoma[5,6,11,15,18]. The characteristic appearance of an osteoblastic lesion is the presence of multiple discrete, or ill-defined areas of increased radiodensity. Normal trabecular architecture is lost when osteoblastic lesions coalesce and mild osseous expansion may ensue. In the spine, diffuse or localized involvement of the vertebrae may produce a sclerotic pedicle or the classic "ivory vertebra". Other processes such as Paget's disease and Hodgkins lymphoma must always be differentially considered[2,4,15,16].

In approximately 10 percent of cases of skeletal metastasis, a mixed pattern may be observed. With this pattern, a combination of bone destruction and reformation, can be noted. Tumors from the breast, lung, kidney and liver may elicit the mottled appearance associated with mixed metastasis. This pattern may also arise following lytic lesion irradiation[4,2].

Nuclear imaging, utilizing radioactive labelled phosphates such as technetium^{99} diphosphonate, is one of the most useful methods of detecting skeletal metastatic disease[8]. Its sensitivity approaches 97 percent and only requires that a 3–5 percent loss of osseous tissue occur prior to a positive detection. It has been estimated that approximately 40 percent of patients with a positive bone scan exhibit normal plain films[6,2]. A positive bone scan reflects immature woven bone which is produced in a futile attempt to repair trabecular resorption. The technetium^{99} diphosphonate is concentrated in the new osteoid produced by the osteoblasts, and is not "taken up" by the tumor cells. The pattern is identified by focal or, more commonly diffuse areas of increased radionuclide accumulation within the skeleton. These "hot" areas on the scan are found in the presence of blastic or lytic lesions and signify accelerated bone production regardless of etiology. For this reason, bone scans should be correlated with the skeletal survey, tomography, computed tomography and clinical laboratory data so that a greater degree of diagnostic specificity can be appreciated. The exception are tumors which are associated with little osseous repair, such as myeloma, which do not result in a "hot" bone scan[2,3,6,8,11,19]. Nuclear imaging has been determined to be a valuable method by which to evaluate treatment regimes but may be somewhat less valuable for the staging of primary tumors[20,21,22].

Computed tomography (C.T.) has proved to be a safe, noninvasive procedure which has provided increased resolution of the two-dimensional detail of tumors. With the development of reconstituted images, an accurate assessment of osseous and soft tissue involvement is possible. The use of C.T. has been especially diagnostic for pelvic, sacral and spinal metastases, where conventional imaging has had limited effectiveness. Along with C.T., magnetic resonance imaging may allow the surgeon to evaluate the feasibility of tumor resection and extent of radiotherapy[3,5,6]. Osseous biopsy remains the only definitive method of determining the presence and origin of metastatic disease, however, it is seldom required to render a diagnosis[3].

Clinical features

Metastatic disease normally favors the older population (usually after the fourth decade) but any age may be affected. Skeletal pain, especially back discomfort, is often the presenting complaint. In fact, the pain, which is usually insidious in onset, is the most common symptom reported. The pain may not always be apparent at night but may be related to physical exertion. Symptoms may be relieved by rest. Pain occurring suddenly or after minor trauma may be resultant from pathological fracture in 15 to 20 percent of patients. Extradural metastatic disease, soft tissue tumor extension, vertebral body collapse or resulting angular spinal deformity may produce lower limb or girdle parasthesia, muscle weakness and loss of urinary or rectal control due to cord compression. This pattern may be experienced in up to 20 percent of patients with spinal metastases. Any indication of neurological compromise may dictate immediate myelographic evaluation[1,3]. The pain, which may also be dull and remittant, may also be associated with normal radiographs. Some patients may be relatively asymptomatic until secondary lesions have already disseminated. Unexplained weight loss, anemia, intermittent pain, fever and cachexia, occur later. Laboratory features including elevated E.S.R., increased serum calcium, elevated alkaline and acid phosphatase are unreliable diagnostic parameters which are seldom required to secure a diagnosis of metastatic bone disease.

It is never unreasonable to assume that a patient can present to a chiropractor with back pain produced by metastatic disease. Patients suffering from skeletal pain with a history of primary malignant neoplasm should always be regarded with the suspicion that they may be harbouring metastatic skeletal lesions. Appropriate history, examination and radiography will usually be rewarding. Immediate referral is warranted if patients provide evidence to the chiropractor that they have, or may have skeletal metastasis. Unexplained skeletal pain in patients with primary malignant tumors in which the usual diagnostic procedures prove fruitless also warrant referral for more elaborate testing and treatment.

Case report

A 42-year old caucasian female presented to a chiropractic office with mild neck pain and stiffness which the patient attributed to poor sleeping habits. The pain was described as getting progressively worse, especially at night. Four years previous she was diagnosed as possessing a benign mass in her left breast. The patient was in otherwise good health.

Examination revealed mild, universal loss of cervical spine range of motion with concomitant production of mild pain and stiffness. Cranial nerve assessment was normal and there was no evidence of neurological deficit. There were no headaches or upper limb symptoms reported. Radiographs of the cervical spine taken by the chiropractor revealed marked osteolytic destruction of the third cervical vertebral body with mild retrolisthesis of C3 relative to C4. (Figure 1) Mild swelling of the paravertebral soft tissues was also apparent.

The patient was immediately referred for medical consultation but did not appear for this appointment since she claimed to be feeling much better and thus felt that there was no need to pursue her condition further. After several weeks the patient again presented to the chiropractor with severe unremitting neck pain which intensified at night. She was immediately referred to a local hospital for assessment. A breast examination revealed a rigid 5 cm. mass in the left breast immediately below the nipple with nipple inversion and peau d'orange. Mammograms exhibited deformity of the left breast with gross indrawing of the nipple, areola and periareolar skin with thickening of the skin of the breast. A 5 cm. mass located above the nipple was suggestive of a large scirrhous carcinoma. (Figures 2 a, b, c,) Plain film radiographs performed by the hospital of the cervical and thoracic spines, pelvis and hips revealed marked destruction of the C3 vertebral body as well as multiple lucent defects within the left pubic bone, right superior pubic ramus, right sacral ala, both ischial tuberosities and the supra acetabular area of the left innominate. (Figure 3) The thoracic spine was reported as being normal.

The whole body bone scan disclosed multiple "hot" spots in the C2-C3 area, thoracic spine, ribs, lower sternum, left ischium and right ala of sacrum. The scan of the brain was negative. Computed tomography of the cervical spine revealed widespread destruction of the inferior third of the C2 vertebral body, C3 vertebral body extending into the left pedicle and lamina, and the superior third of the C4 vertebral body. Some mild encroachment upon the anterior aspect of the dural sac on the left at the C3 vertebral level was also noted. (Figure 4a, b).

The patient received a left radical mastectomy and was treated by anterior decompression with stabilization of her cervical spine from C2 to C5. The patient also underwent chemotherapy and radiation therapy. In spite of this type of intensive management, the prognosis, unfortunately, remains poor.

Figure 1 Third cervical vertebral body osteolysis with mild retrolisthesis of C3 on C4.

Conclusion

In conclusion, this case serves to illustrate that it is not unreasonable to assume that patients with back pain of insidious onset will be presenting to our offices. As these individuals become more aware of the roles being played by chiropractors within the health care system and as their confidence in our skills and abilities become enhanced, they will be presenting with a vast array of conditions, the least of which may be metastatic disease. As chiropractors, we have the moral, legal and ethical obligations to live up to their expectations.

Acknowledgement

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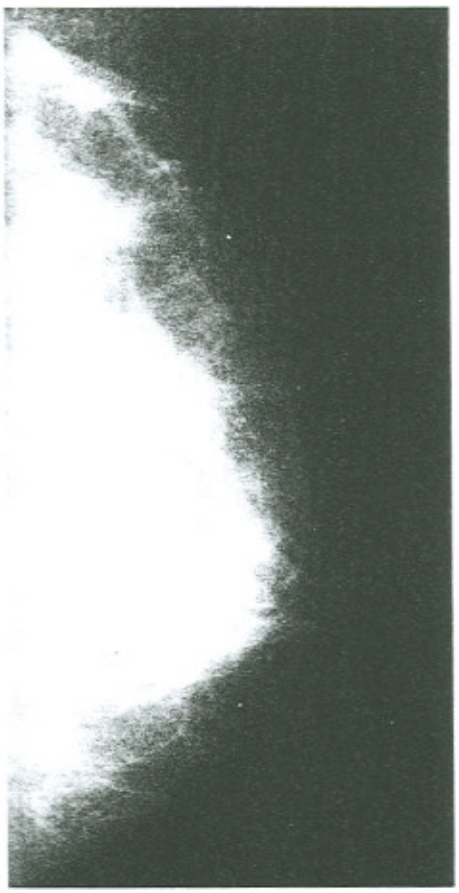

Figure 2a Normal right breast stromal formation.

Figure 2b Large 5 cm. mass adjacent to the nipple suggestive of scirrhous carcinoma.

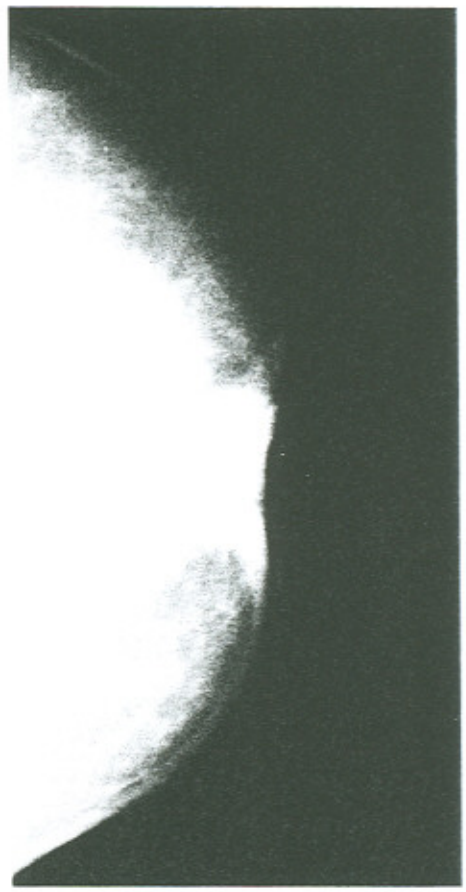

Figure 2c Marked inversion of the nipple, areola and periareolar cutaneous thickening.

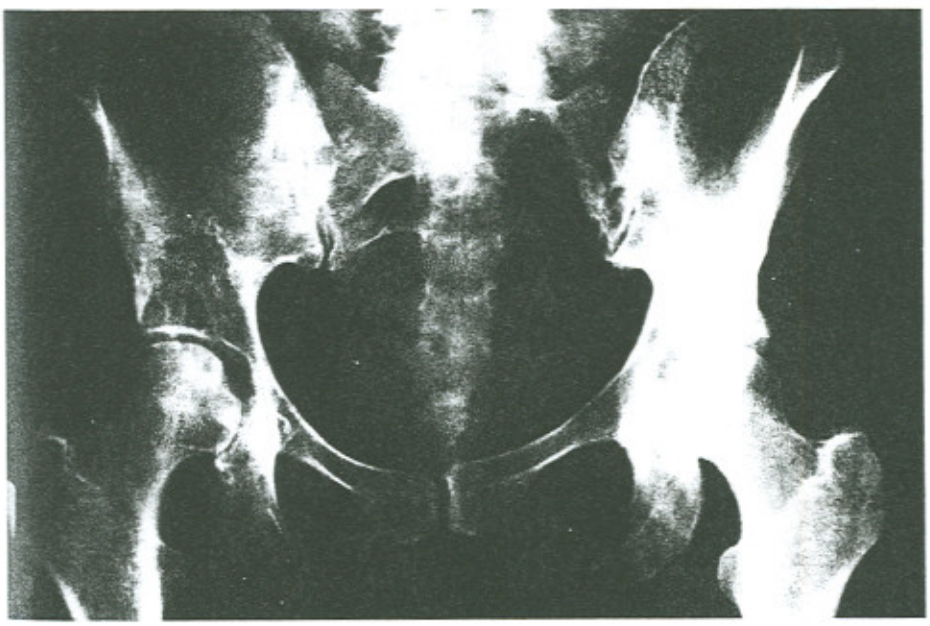

Figure 3 Multiple radiolucent defects observed within the right pube, superior pubic ramus, sacral ala, supra acetabular region and ischial tuberosities bilaterally.

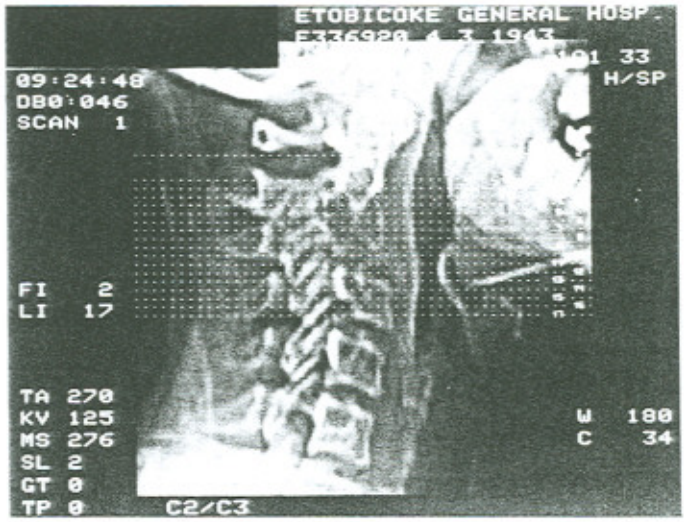

Figure 4a Reference study in the sagittal plane through the cervical spine.

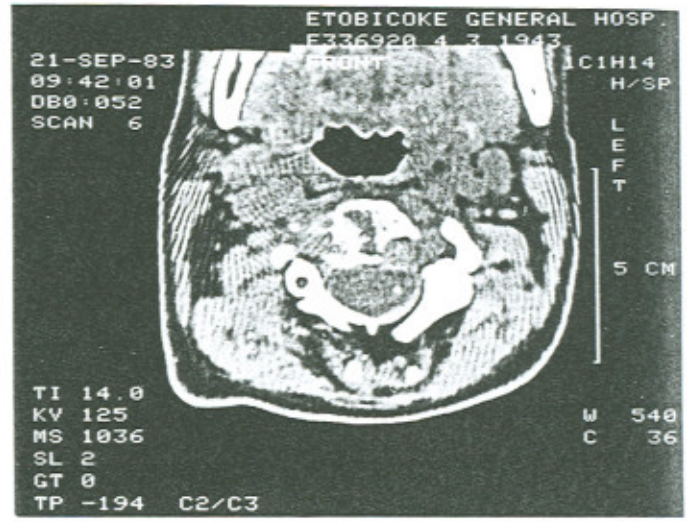

Figure 4b C.A.T. through C3 revealing widespread osseous destruction including the left pedicle and lamina. A suggestion of encroachment upon the anterior aspect of the dural sac on the left at the level of C3 is also observed.

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