University of Calgary Combined Neuroscience Rounds

Clinicopathological Conference Carcinoma of the Pituitary Gland with Metastases to Bone

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ABSTRACT: The diagnosis of extracranial metastases from a pituitary tumor was confirmed by the use of the immunoperoxidase technique. This is believed to be the first case of carcinoma of the pituitary gland with bony metastases where the diagnosis has been confirmed in that manner.

RÉSUMÉ: Nous avons confirmé le diagnostic de métastases extra-crâniennes d'une tumeur pituitaire par l'emploi de la technique d'immunopéroxydase. On croit que c'est le premier cas d'une carcinome de la glande pituitaire avec des métastases dans l'os où le diagnostic a été montré à cette façon.

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Case Report

Six years before death, this 56 year old female presented to her family doctor with right periorbital pain. She had had a history of recurrent right frontal headache for 7 years. This was described as a nonspecific pain, beginning at the inner canthus of the right eye. The pain would quickly worsen and extend to involve the entire right side of the forehead, and the right side of the nose would feel full or "tingle". Vomiting would usually follow and then she would notice her right eyelid drooping and occasionally swelling around the right orbit. Furthermore, she stated she would be unable to move her right eye in any direction, although she did not complain specifically of diplopia. Analgesics would provide little relief of this pain and, in fact, sleep was the only alleviating factor. The pain generally lasted 3 to 4 days and then gradually disappeared. However, the right ptosis and ophthalmoplegia would persist for 2 to 3 weeks before gradually resolving.

These episodes had occurred only once per year, usually in the autumn. She previously had been investigated in another institution and apparently had had 3 normal angiograms. She had been given methysergide and prednisone during episodes of pain. The current episode had followed the characteristic pattern, and she consulted her physician after 3 days of headache.

Past history included an appendectomy, a right oophorectomy for ovarian cyst, and a left salpingectomy for ectopic pregnancy. She had undergone a hysterectomy for menorrhagia 4 years previously. The patient was a nonsmoker. Family history revealed only that a sister had died of leukemia. No family members suffered from headache.

Her family doctor's physical examination revealed a dilated but reactive right pupil and a right ptosis. Right eye movements were restricted in all directions but most markedly in the vertical plane. A right-sided upper temporal visual field defect was detected. At the time of admission to a tertiary care hospital, 2 days later, the headache had resolved. Examination showed an obese, pleasant 56 year old female. Pulse was 78 and regular. Temperature was 36.8°C, bloodpressure 145/85. General examination was normal except for edema around the right orbit and perhaps slight proptosis. Neurological examination showed a fixed right pupil of 3.0 mm and right ptosis. The resting eye position was straight forward but there was little movement of the right eye in any direction. The left eye moved normally. No visual field defect was noted. Decreased pinprick sensation was detected over the right forehead. The neurological examination was otherwise normal.

Investigations showed: hemoglobin 116g/l., white blood cells 17,300 per mm^3 with a normal differential; erythrocyte sedimentation rate 58 mm/hr.; urinalysis — normal; SMA6 and SMA12 — normal; and plasma T_4 77.2 n mol/l. CSF examination was also normal. Goldman perimetry showed normal visual fields.

Skull roentgenograms showed a somewhat sclerotic posterior sella turcica. Angiography revealed minimal findings compatible with a right parasellar mass. Computed tomography (CT) disclosed a small irregular mass of increased density, with enhancement, on the right side of the suprasellar region. Pneumoencephalography showed a plum sized mass in the right side of the pituitary fossa extending posteriorly and superiorly, indenting the right lateral wall of the 3rd ventricle. A surgical procedure was then performed. Postoperative recovery was unremarkable. She was discharged home with a residual right oculomotor nerve palsy.

She was readmitted 9 months later with recurrent right periorbital and head pain and right periorbital swelling, heavy tearing, and clear nasal discharge. On this occasion, she also reported numbness involving the right upper lip, the right buccal mucosa and teeth, and the right lower jaw. At this time examination revealed normal vital signs. There

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was right periorbital edema with slight proptosis and ptosis. The right eye was tearing profusely. Olfaction was intact bilaterally. The right pupil was fixed and slightly ovoid measuring 3.0 mm in diameter. Ocular fundi were normal. Visual acuity and visual fields were normal. Total right ophthalmoplegia, except for slight lateral movement, was noted; left eye movements were normal. Complete sensory loss was noted over the right V_1 to V_3 dermatomes, and there was a question of right masseter and right pterygoid weakness. The remainder of the cranial nerves and neurological examination was normal. Serum sodium was 147 m Eq/l, and chloride was 105 m Eq/l. Otherwise, the SMA6 and SMA12 were normal. Specific gravity of the urine was 1.031.

Skull x-ray and CT were repeated and showed evidence of a residual enhancing lesion in the right suprasellar region. Roentgenograms of the paranasal sinuses were normal. Visual perimetry again was normal.

She underwent a course of radiotherapy with disappearance of her head pain and, over a period of months, considerable improvement in her cranial nerve findings.

Eighteen months from the time of craniotomy, the patient was readmitted with intermittent crampy low back pain of 4 days duration. She stated these resembled menstrual cramps but were aggravated by movement. Mild analgesics did not relieve this pain. A separate complaint was a crampy lower abdominal pain of similar duration. This radiated from the RLQ to the midline area, and was relieved with a hot water bottle. She denied bladder or bowel complaints or any lower limb symptoms. A weight loss of 6 kg. over the previous year was noted.

Physical examination again showed a residual oculomotor nerve palsy. However, the trigeminal nerve was normal as was the remainder of the neurological examination. There was mild tenderness over the left 11th and 12th ribs posteriorly and over the left sacroiliac joint. Moderate nonpitting edema was noted in both ankles. The examination was otherwise normal.

Radiographs showed sclerotic lesions involving several vertebrae and pelvic bones. Bone scan showed increased uptake in these same areas. Skull x-ray had not changed. Bilateral mammograms, IVP, UGI series and scans of thyroid and liver were normal. Pituitary function tests were carried out and revealed mild panhypopituitarism.

A biopsy of left posterior iliac crest was done. The back pain resolved spontaneously and she was discharged home.

Despite evidence of extensive osteoblastic bone lesions, she remained asymptomatic over the next six months, although she lost a further 2.7 kg. and became mildly cold intolerant. Investigations showed a T_4 — 30.9 n mol/l; free thyroxin index 57.4. She was started on Thyroxin and Cortisol.

Two and a half years from the time of craniotomy, she developed sacral pain and was treated with palliative radiotherapy.

She was followed by her family doctor over the next 2 years, with her main problems being pain in her legs and back, and progressive weight loss. Approximately 6 months prior to death, she was admitted to her local hospital with a left flaccid hemiparesis, coma and seizures. She apparently recovered from this and was alert and lucid until 5 days before death when she again became comatose. She died 6 years from the time of craniotomy and 13 years from the onset of symptoms.

Discussion

Clinical Features (Dr. Myles)

The patient had a history of unilateral right periorbital pain of 7 years' duration which was intermittent and associated with vomiting and ophthalmoplegia. Investigation was carried out elsewhere and presumably a diagnosis of ophthalmoplegic migraine was made, judging by the treatment with methysergide and prednisone during attacks.

At the time of admission to the tertiary care hospital, the patient had paralysis of the right 3rd, 4th, and 6th cranial nerves and involvement of the ophthalmic division of the 5th cranial nerve. Vision was normal, and there was a suggestion of proptosis and edema around the orbit. On the basis of these findings, a review of the appropriate anatomy (figure 1) shows that the lesion can be localized to the right anterior cavernous sinus or the superior orbital fissure.

During her subsequent hospitalization 9 months later she had recurrent right-sided head pain, evidence of parasympathetic nerve irritation with excessive tearing and nasal discharge, and complete loss of 5th cranial nerve sensory function. There was questionable involvement of the motor component of the trigeminal nerve, and vision remained normal. A review of Jefferson's (1938) diagrams of the cavernous sinus (figure 2) shows that the pathological process must have extended posteriorly to produce this clinical picture.

The patient later progressed to develop low back and lower abdominal pain. The distribution of the abdominal pain suggested referred pain from irritation of the right T12 or L1 nerve roots.

About six months prior to her death she was hospitalized because of a left flaccid hemiparesis, coma and seizures, from which she recovered. One can speculate that the patient developed a right central cortical irritative lesion, causing focal seizures which became generalized resulting in coma and a postictal transient left hemiparesis. A lesion causing transient compression or ischemia of the right side of the midbrain could cause coma and left hemiparesis, and seizures could have occurred as a secondary phenomenon. Further expansion of a lesion in this location could explain the terminal coma and death.

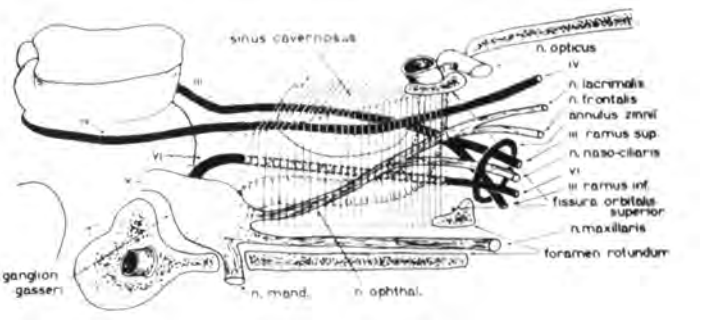

Figure 1 — Diagram of the superior orbital fissure and the cavernous sinus. (Lakke, 1962 — reproduced with permission)

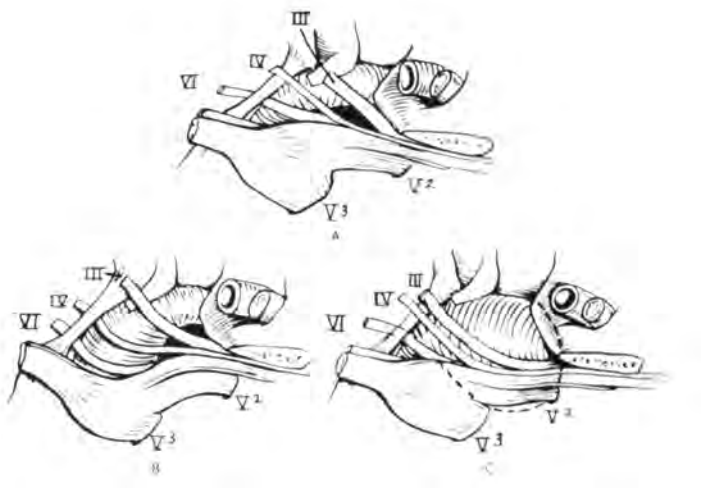

Figure 2 — Diagrams of the anatomical syndromes of the cavernous sinus. A, Normal; B, Syndrome of posterior end of cavernous sinus; C, middle syndrome of cavernous sinus. (Jefferson, 1938 — reproduced with permission)

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In summary, on anatomical grounds the patient had a lesion in the right superior orbital fissure or anterior part of the cavernous sinus, which subsequently extended to the posterior end of the sinus. There may have been further posterior and medial extension from this location to cause midbrain compression. A separate lesion in the spine caused irritation of the T12 or L1 nerve roots.

Radiographic confirmation of a parasellar lesion and multiple osteoblastic skeletal lesions (refer to Radiological Aspects) leads to consideration of the pathological diagnoses which can give this picture. Though the patient may have had 2 separate pathological entities, it would be nice to relate the clinical picture to one diagnosis.

The superior orbital fissure syndrome which the patient demonstrated on admission, can be caused by trauma, inflammation which may be specific (tuberculous meningitis, syphilis) or nonspecific (Tolosa-Hunt syndrome) or due to vascular anomalies such as internal carotid artery aneurysms or fistulae (Lakke, 1962). The clinical course and radiographic studies are not consistent with these diagnoses, but could be due to neoplasm which also can produce the syndrome.

Parasellar tumors may be primary arising from bone, meninges, the pituitary gland or cerebral tissue. They may also be metastatic, arising from local spread from the nasopharynx or from distant sites (Thomas and Yoss, 1970).

The presence of osteoblastic skeletal lesions makes benign parasellar tumors such as craniopharyngioma, neurofibroma or meningioma unlikely. A malignant meningioma with subsequent metastasis is possible. However, meningiomas arising in the cavernous sinus are very uncommon (Jefferson, 1953) and metastases from malignant meningiomas are usually found in the lung or liver (Karasick and Mullan, 1974).

The most common cause of the parasellar syndrome in Thomas and Yoss's (1970) report of 102 cases was local spread of nasopharyngeal tumor. Jefferson (1953) also found that nasopharyngeal carcinoma was the tumor most commonly involving the cavernous sinus and he emphasized the frequency of trigeminal nerve involvement. Nasopharyngeal carcinoma with metastases is a possibility in this patient, as spinal metastases may occur. The relatively long clinical course, absence of enlarged cervical lymph nodes and lack of bony erosion or nasopharyngeal soft tissue mass on radiographs of the skull and sinuses make this diagnosis less likely.

A metastatic parasellar neoplasm could have caused this patient's clinical picture. In a woman, the tumor would most likely have come from breast, lung or the intestinal tract. The thyroid gland is another possible primary site. Occult malignancies in any of these locations are occasionally found only after the patient becomes symptomatic with intracranial metastases. Any of these tumors may spread to the bony skeleton. However, there were no clinical signs of any of these tumors over a 6 year time interval from the initial presentation. Osteoblastic metastases may occur with pancreatic and breast carcinoma but are uncommon with lung and thyroid tumors. (Edeiken, 1981). Also, the absence of any evidence of tumor involvement of breast, lung, intestinal tract or thyroid gland on radiographic studies or nuclear scans makes these diagnoses unlikely.

If an obviously malignant tumor had been found at the time of craniotomy, I would have expected the patient to have immediate postoperative radiation therapy, as the tumor removal was incomplete. The fact that radiation therapy was not used until after her tumor recurrence 9 months later makes me suspect that there was doubt about the malignant nature of the lesion. The sequence of events therefore makes other malignant parasellar tumors such as lymphoma, melanoma or myeloma very unlikely.

Chordoma should also be mentioned in the differential diagnosis, as it can involve the base of the skull, cause cranial nerve palsies, and produce metastases to bone (Kamrin et al., 1964). However, the bony lesions are usually osteolytic, unlike the present case.

Histiocytosis X should be considered in the differential diagnosis of parasellar lesions, and skeletal lesions are common in this syndrome. About 50% of patients with this syndrome will have diabetes insipidus and the skeletal lesions are osteolytic, so the possibility of this diagnosis seems very low.

The other group of tumors which may present as parasellar masses and have cavernous sinus involvement are the pituitary adenomas. It has been estimated that 4% or 5% of pituitary adenomas break through into the cavernous sinus and become locally invasive (Jefferson, 1953). Burger and Vogel (1982) have stated "neither the aggressiveness of the lesion nor the tempo of recurrence can be predicted reliably from the histopathologic features in cytologically benign growths."

The clinical course in this patient could have been caused by an aggressive pituitary tumor. The patient was not given radiation therapy initially because the tumor looked histologically benign. Only after she presented with evidence of involvement of the second and third divisions of the trigeminal nerve was the aggressive nature of the tumor appreciated. Jefferson (1940) emphasized that trigeminal anesthesia meant that a pituitary adenoma had broken into the cavernous sinus, and was a criterion of malignancy.

The development of panhypopituitarism in the patient also was consistent with expansion of a nonsecreting pituitary tumor.

Pituitary tumors may rarely spread beyond the cranial cavity, and in this situation may be termed carcinoma. Intracranial extension and cavernous sinus invasion has usually been associated with these tumors, as in the present case.

Spread of pituitary carcinoma to the lumbar spine has been reported (Epstein et al., 1964) as well as metastases to the liver (Graf et al., 1962). Jefferson (1940) reported operating on a tumor invading the sixth thoracic vertebra that was returned histologically as a pituitary adenoma. I was unable to find any reports of osteoblastic spinal metastases from pituitary carcinoma.

Symptomatic improvement following radiation treatment of the metastases, as noted in the present patient, was described by Epstein et al. (1964).

A final diagnostic consideration to be mentioned is the multiple endocrine neoplasia (Wermer) syndrome. About two-thirds of patients have adenomas of two or more endocrine systems, and pituitary adenomas may be part of this syndrome. Unlike our present patient, most patients have peptic ulcer problems, hypoglycemia, hypercalcemia, multiple cutaneous lipomas and a positive family history in addition to the pituitary involvement. Multiple pancreatic or adrenocortical tumors may develop. Metastasis to bone from an occult malignancy of this type was a consideration in this patient, but for reasons already given was thought to be less likely than carcinoma of the pituitary gland with metastases.

My final diagnosis is pituitary carcinoma with local extension, cavernous sinus invasion and distant metastases to bone.

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Radiological Aspects (Dr. Johns)

The patient had multiple radiologic investigations during the course of her illness.

Initial skull radiographs revealed minimal erosion of the posterior clinoids and tip of the dorsum sellae associated with poorly marginated bony sclerosis of the dorsum and posterior wall of the sella turcica. The sella turcica was of normal volume and configuration and the skull was otherwise unremarkable.

Computed cranial tomography (CT) demonstrated an irregular radiodense lesion involving the suprasellar cistern, growing predominantly to the right of the midline and exhibiting uniform contrast enhancement (figure 3).

Cerebral angiography and pneumoencephalography confirmed the presence of a mass lesion embracing the dorsum sellae and extending superiorly into the suprasellar and interpenduncular cisterns.

The patient then underwent craniotomy.

Nine months later another CT demonstrated a residual mass at the site of the previously demonstration lesion. The mass was judged to have not significantly increased in size in the interval. Skull radiographs demonstrated persistent sclerosis of the dorsum sellae.

Eight months later a Tc99m — polyphosphate bone scan demonstrated focal increased uptake of the radiopharmaceutical at T12 and L2 and in the right posterior parietal region (figure 4). Radiographs of these regions revealed dense osteosclerosis involving the body and pedicles of T12, a large portion of the body of L2, (figure 5) and a large focus of osteosclerosis in the right parietal bone.

Subsequent radiographs of the cervical spine, lumbar spine, and pelvis obtained 9 months later demonstrated widespread osteoblastic lesions throughout the visualized bony skeleton (figure 5).

Pathology (Dr. Curry)

At the time of the original right fronto-temporal craniotomy, a number of small friable, rather hemorrhagic tumor fragments were submitted for histopathological examination. The biopsy material showed a vascular tumor with a rather sinusoidal pattern and composed of relatively uniform small cubical cells with clear or slightly granular cytoplasm. The presence of the occasional mitotic figure and a small number of bizarre pleomorphic looking giant and multinucleated cells was noted. It has long been recognized (Kernohan, 1956; Kovacs, 1979; Burger, 1982) that the presence of mitotic figures and cellular pleomorphism in pituitary adenomas are not good indicators of the subsequent biological behaviour of pituitary adenomas. In the absence of modern current morphological techniques, this was reported as a chromophobe adenoma.

Eighteen months later, a biopsy was taken from the patient's posterior iliac crest. The histological sections showed a very vascular tumor with relatively large clear cells, no mitotic figures and little nuclear pleomorphism. The surrounding bone showed a marked osteoblastic reaction. In view of her previous history, it was considered that this could well be a metastic tumor from a primary endocrine carcinoma, but, more common primary tumors should first be excluded. In an attempt to discover another primary tumor, extensive investigations including a breast biopsy, were carried out. The latter biopsy proved to be benign.

Following this patient's death at the age of 62 years, an autopsy was performed at the local hospital where she had died. The scalp was described as very adherent to the calvarium on the external surface and the dura adherent to the internal surface at the site of the original fronto-temporal craniotomy. Most of the rest of the calvarium was greatly thickened, up to 2.5 cm in places. The bone had an opaque white appearance

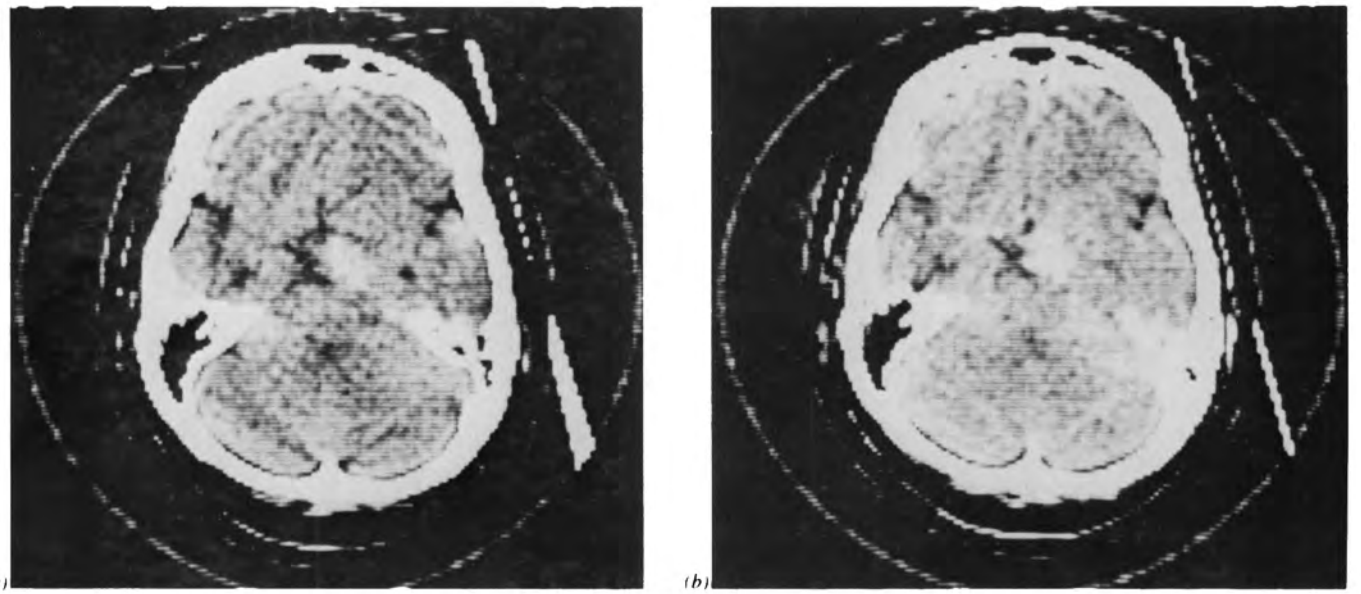

Figure 3 — (a) C.T. scan of head — nonenhanced (b) C.T. scan of head — contrast enhanced.

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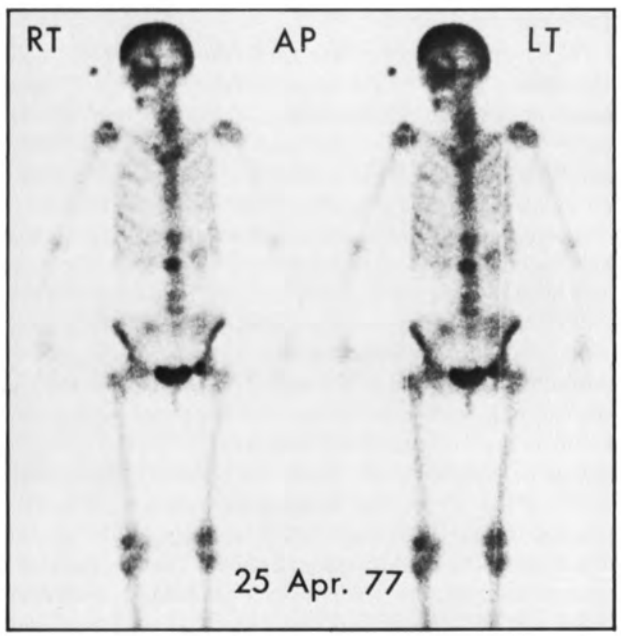

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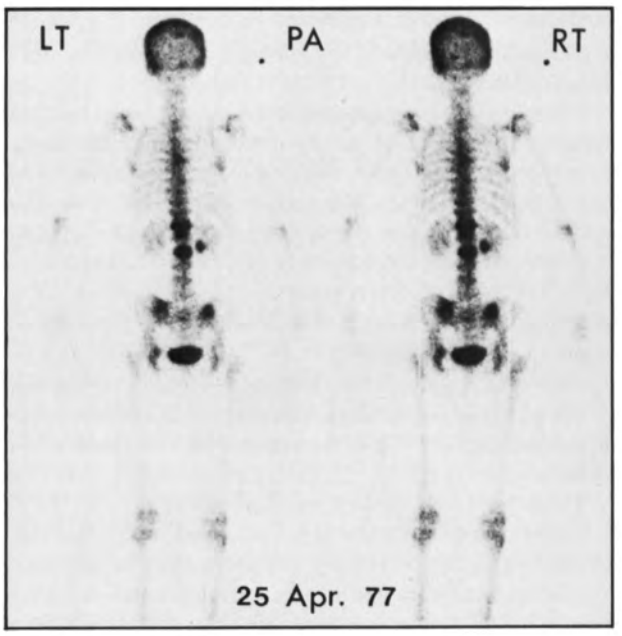

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Figure 4 — (a) Tc99m — polyphosphate bone scan — AP view (b) Tc99m — polyphosphate bone scan — PA view

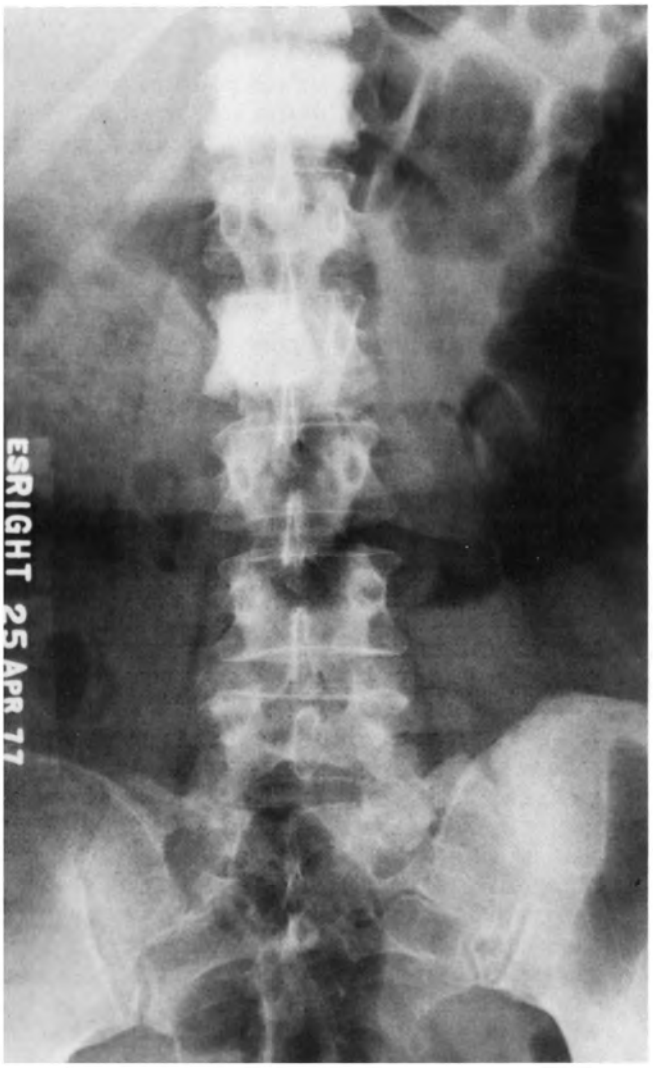

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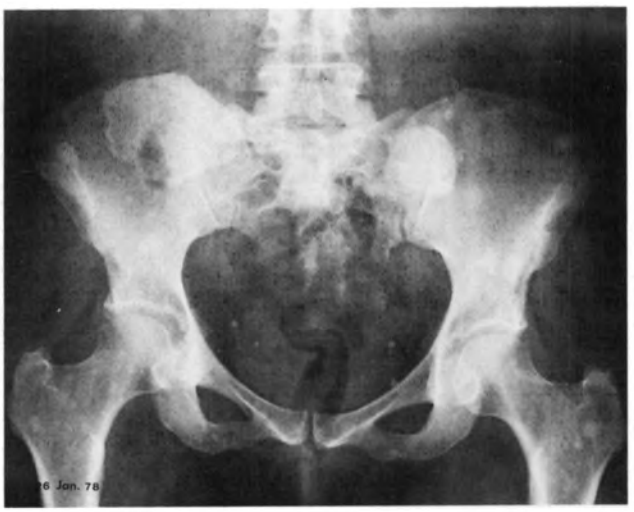
Figure 5 — (a) Radiograph of lumbar spine — AP view (b) Radiograph of pelvis.



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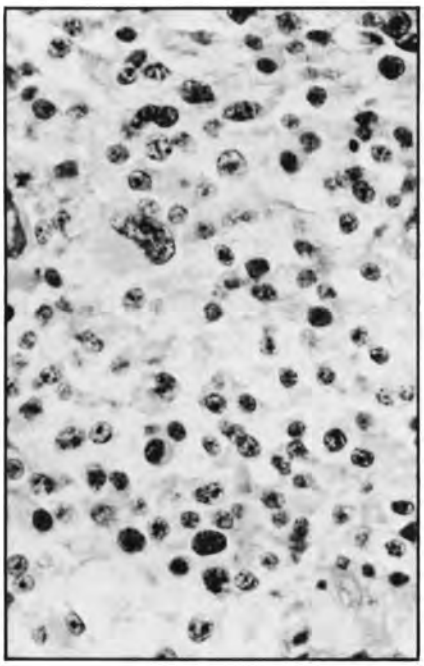

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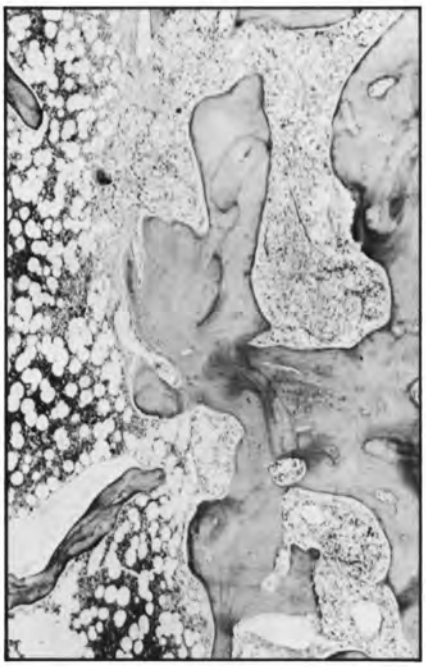

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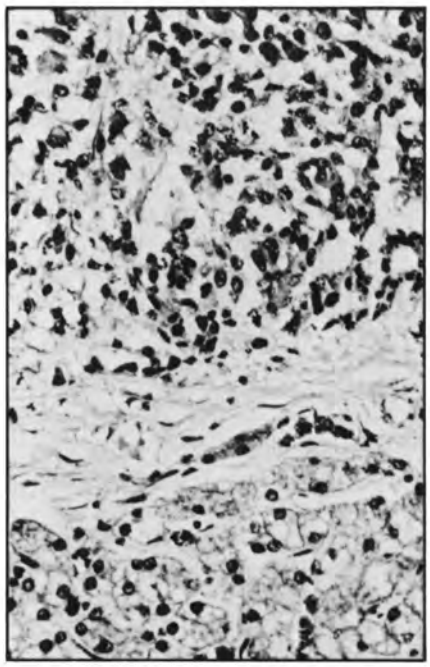

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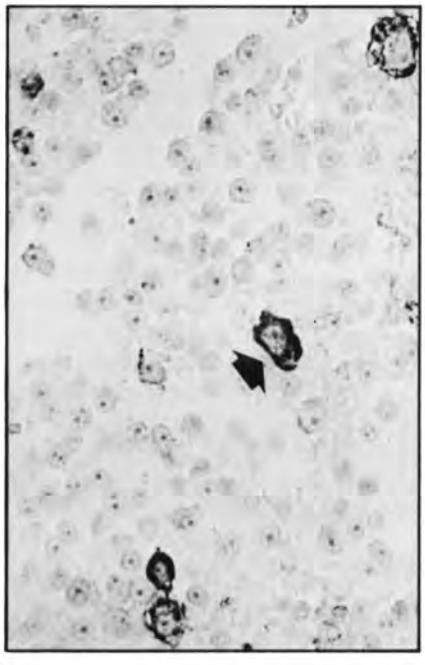

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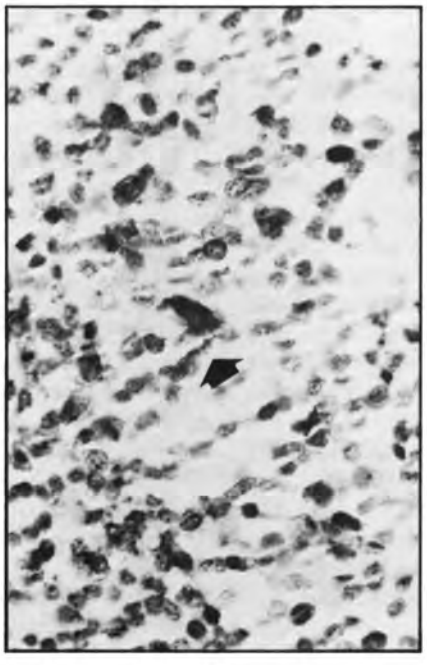

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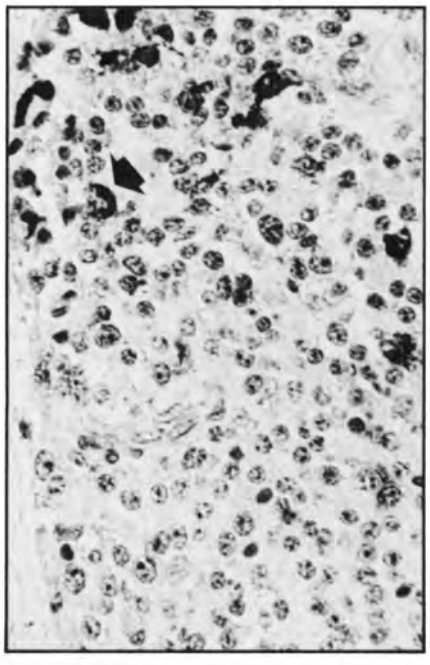

(b)

Figure 6 — (a) Original pituitary tumour. Occasional pleomorphic cells are seen. H&E x 160 (orig. mag.) (b) Immunoperoxidase Technique showing granular deposits of immunoreactive growth hormone in cell cytoplasm (arrow) of original pituitary tumor. H&E x 160 (orig. mag.)

Figure 7 — (a) Metastatic carcinoma in iliac crest. Note marked osteosclerosis of bone. H&E x 3.2 (orig. mag.) (b) Immunoperoxidase technique showing immunoreactive growth hormone in cells (arrow) of bony metastasis. H&E x 128 (orig. mag.)

Figure 8 — (a) Metastatic carcinoma in liver. H&E x 80 (orig. mag.) (b) Immunoperoxidase technique showing immunoreactive growth hormone (arrow) in cells of liver metastasis. H&E x 128 (orig. mag.)

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and the skull was only opened with great difficulty as the bone was as hard as marble. Adherent to the inner surface of the dura were three cauliflower shaped tumors. All were described as being adjacent to the midline. Each of these tumors caused indentation of the underlying brain. The largest (8 × 5 × 4 cm) overlay the left mid-frontal lobe; the second (3 × 2 × 2 cm), the right frontal lobe; and a third one (3 × 2 × 2 cm), the left occipital lobe. Both frontal lobe tumors were so situated that they could well have been expected to produce focal neurological signs and probably seizures. The largest tumor contained areas of hemorrhage and extensive areas of necrosis. Examination of the base of the skull showed a normal sized pituitary fossa; the right posterior clinoid process was absent. The bone in this region was also extremely sclerotic. The pituitary fossa itself was almost empty; the residual material from the floor of the fossa and the surrounding area were taken for histology. The entire vertebral column and pelvis was extensively osteosclerotic and marble hard. A number of samples were taken for histological examination. There was no obvious involvement of the ribs and the long bones were not examined. The brain and the spinal cord showed no evidence of metastatic tumor.

The endocrine organs, including the thyroid gland, parathyroid glands, the adrenals and the pancreas were carefully examined for evidence of one or more minute tumors. None were found. A few small (0.5 to 1.0 cm in diameter) metastatic deposits were scattered throughout the liver. Both breasts were examined in detail but no evidence of tumor was detected. The uterus and left ovary had previously been removed. All the other organs in the body showed no significant pathological findings.

Material from the autopsy, in the form of blocks and sections of dura, pituitary fossa and surrounding area, liver, skull and vertebral body was referred from the local hospital for consultation with a request that it be reviewed together with the original biopsy material. The microscopic appearance of the tumor in the dura and liver was very similar to that of the original pituitary tumor. There were very few mitotic figures and only scattered pleomorphic cells. Only in the dural lesions were there areas of necrosis. The tissue from the base of the skull showed residual tumor cells. Pleomorphism was much more marked here and this presumably was due to irradiation of this area. There was infiltration of the dura, cavernous sinus and trigeminal ganglion. The presence of metastatic carcinoma in the densely sclerotic calvarium and vertebral bone also was confirmed.

It should be emphasized that though there was microscopic evidence of residual tumor in the region of the pituitary fossa, there was no massive local recurrence. Little detail was available about the onset of left hemiparesis, seizures and coma, six months before death or of the terminal five days of coma. However, large subdural metastases, particularly those overlying and indenting the frontal lobes, were the likely precipitating factors for these two incidents. Osteosclerotic narrowing of the intervertebral foramina was the most likely cause of her back and leg pain.

The introduction of the immunoperoxidase technique since the time of the original pituitary and bone biopsies allowed that material to be reviewed in conjunction with the autopsy tissue in greater morphological detail. Sections of the original pituitary tumor, the posterior iliac crest biopsy, one of the dural metastases and one of the liver metastases were tested, using this technique, for the presence of human growth hormone, prolactin, ACTH, luteinizing hormone and follicular stimulating hormone, gastrin and glucagon. The sections from all tumor sites proved to be negative for all hormones except human growth hormone. Positive granules of immunoreactive growth hormone were found in the cytoplasm of some tumor cells in the original pituitary tumor (Fig. 6a & 6b), in the posterior iliac crest metastatic tumor (Fig. 7a & 7b), in the dural metastasis, and in the liver metastasis (Fig. 8a & 8b). Electron microscopy was carried out on some of the paraffin-embedded pituitary tumor. The subcellular structure was extremely poorly preserved, though the appearance of the tumor cells and the presence of scattered secretory granules was in keeping with a sparsely granulated tumor of the anterior pituitary.

The use of the immunoperoxidase technique in the present case illustrates its value in confirming this unusual diagnosis of primary pituitary carcinoma with subdural seeding and extracranial metastasis. It has been considered that the diagnosis of carcinoma, with reference to tumors of the anterior pituitary gland, should only be used where the presence of extracranial metastasis can be demonstrated (Martins, 1965; Kovacs, 1979; Burger, 1982). Local invasion, even if there is extensive involvement of contiguous structures (Martins, 1965; Wilson, 1982) or seeding confined entirely to the subarachnoid (Epstein, 1964) or subdural space (Ogilvy, 1973), does not indicate true malignancy. Using these criteria, carcinoma of the anterior pituitary gland is extremely rare. Zulch (1965) doubted that such cases occurred; he considered many of the earlier reports in the literature to be unconvincing, while Willis (1967) considered that only two of the cases reported to that date were acceptable. The most recent case report (Queiroz, 1975) of a pituitary tumor with extracranial metastasis, included a review of the proved cases with blood-borne or lymph node metastases. In addition to his own, there were 12 such cases, though one of these had been considered unconvincing by Zulch. Most cases had metastases in the liver (nine); only in one case was bony metastasis mentioned. Surprisingly, six were associated with Cushing's Syndrome; the remainder appeared to have nonfunctional tumors. The diagnosis in all cases was made at autopsy and was based on the histological similarity of pituitary and extracranial tumors, and the absence of another primary lesion. The rarity of this lesion is emphasized by the fact that there appears to be no more recent report in which use has been made, as in the case under discussion, of the immunoperoxidase technique to confirm such a diagnosis. Although insufficient human growth hormone was secreted into the blood stream to be detected clinically, one can speculate that perhaps the tremendous osteoblastic effect related to the bony metastasis was induced by a localized increase in human growth hormone.

Anatomical Diagnosis:

Pituitary carcinoma (sparsely granulated growth hormone tumor) with:

a) local invasion of cavernous sinus and trigeminal ganglion.

b) seeding to intracranial subdural space.

c) metastasis to axial skeleton (extensive and osteoblastic) and liver.

ACKNOWLEDGEMENT

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