Ectopic pinealoma: an unusual clinical presentation and a histochemical comparison with a seminoma of the testis

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SUMMARY A patient with ectopic pinealoma first presented with apparent anorexia nervosa and hypernatraemic coma. A history of diabetes insipidus two months previously was not known on admission to hospital. The diabetes insipidus was unmasked by the administration of steroids. Neuroendocrinal and neuropathological aspects of the case are discussed with reference to the march of symptoms due to the growth of the tumour. Histochemical evidence is presented supporting the similarity between ectopic pinealoma and seminoma which suggests that they may more properly be referred to as atypical teratomas.

The first case of ectopic pinealoma was described by Stark in 1928; the patient exhibited diabetes insipidus, visual disturbance, and anterior pituitary insufficiency, which have since become recognized as a typical neuroendocrine triad associated with such a tumour. The initial symptom is usually diabetes insipidus and of the cases reviewed by Rubin and Kramer (1965) and in subsequent case reports (Beaufils, Chapman, and Nedeý, 1968; Ghatak, Hirano, and Zimmerman, 1969; Vejajiva and Sitprijá, 1969; Schrub, Dubnisson, Hellemand, and Leroy, 1970; Kageyama, 1971; Sohn and Pittman, 1971) overt diabetes insipidus was present in 37 of the 41 patients described. Vejajiva and Sitprijá (1969) were the first to describe ectopic pinealoma with hypernatraemia in the absence of diabetes insipidus. Other uncommon features described as a result of hypothalamic involvement are disturbance of temperature regulation, hyperphagia, and anorexia.

This paper describes a patient with a diagnosis of anorexia nervosa who presented in hypernatraemic coma and in whom diabetes insipidus was unmasked by administration of steroids. At necropsy she was shown to have an ectopic pinealoma.

The derivation of such tumours has aroused considerable interest. They have been thought by

various authors to be closely related to the seminoma of the testis and to dysgerminoma of the ovary. Hence, they have been called germinomas and atypical teratomas. In view of the fact that a fresh specimen of tumour became available from a second case, it was felt that, by comparing a variety of histochemical stains on the ectopic pinealoma, a seminoma of the testis, and the normal pineal gland, some evidence might be found to support either a pineal or germinomatous origin for this tumour.

CASE REPORT

In September 1971 a 22 year old single girl, who worked as a children's nanny, was admitted to hospital semi-comatose. The history available on admission was that in her early teens when 168 cm (5 ft 6 in.) tall and only 50.4 kg (8 st) in weight, she considered herself overweight and went on a strict diet. Menarche occurred normally at 14 years of age but menses ceased in August 1970. In September 1971 she became severely anorectic with resulting weight loss after she learned that her father had an inoperable carcinoma of the bronchus (Fig. 1). A diagnosis of anorexia nervosa was made at psychiatric consultation and treatment with tranquilizers and cyproheptadine resulted in improved appetite and slight weight gain. For one week before admission she complained of headaches and dizziness, and progressively became drowsy.

FIG. 1. Photograph of the patient showing the severe state of anorexia.

FIG. 2. Radiograph of the chest showing soft patchy opacities at the apex of the right lung.

EXAMINATION On admission she was semiconscious, emaciated, dehydrated, and pyrexial (38°C). The pulse rate was 100/minute and the blood pressure 95/60 mmHg. Her skin was pale and waxy; pubic and axillary hair was scanty. There was slight neck stiffness but no localizing neurological signs.

INVESTIGATIONS Preliminary investigations revealed anaemia, hypernatraemic dehydration, an apparent lymphocytosis in the cerebrospinal fluid (CSF) and soft patchy opacities at the apex of the right lung on the radiograph of the chest (Fig. 2).

PRELIMINARY LABORATORY RESULTS Initial investigation showed: haemoglobin, 72% (iron deficient on film); leucocyte count, 10,000/cmm (normal differential); platelets 70,000/cmm; ESR 90 mm/hr (Westergren); serum sodium 185 mEq/l.; serum potassium 3.1 mEq/l.; serum bicarbonate 27 mEq/l.; blood urea 66 mg/100 ml., and blood sugar 65 mg/100 ml.

Examination of a mid-stream specimen of urine showed a specific gravity of 1.010, a trace of albumin, no sugar, a positive test for ketones and no organisms. At lumbar puncture the cerebrospinal

FIG. 3. Variation of serum sodium in relationship to treatment given.

FIG. 4. Variation in serum osmolality in relationship to treatment given.

fluid showed a pressure of 150 mm water, white cell count 38/cmm (95% lymphocytes, 5% polymorphs), red cell count 7/cmm, protein 70 mg/100 ml., sugar 55 mg/100 ml., and a negative Lange curve. Stains for bacteria including acid-fast bacilli were negative.

In view of the hypernatraemia, an intravenous infusion of 5% dextrose was immediately started and intravenous hydrocortisone was given as supportive therapy. Opacities in a radiograph of chest and the cells in the CSF suggested a diagnosis of tuberculosis and, therefore, streptomycin, isoniazid, and rifampicin were administered whilst further investigations were in progress. On this therapy, including continued hydrocortisone 100 mg daily, there was

only a marginal improvement in the electrolyte and clinical state. Though the volume of intravenous fluid was progressively increased to 6 l./day, the urine output persistently outstripped input.

It now became clear that she had developed diabetes insipidus and her clinical and biochemical state began to improve only when subcutaneous pitressin was administered.

Further investigations revealed reduced gonadotrophin production and thyroid hypofunction. Radiographs of the skull showed a normal pituitary fossa; echogram showed a central 8 mm third ventricle; electroencephalography (EEG) showed widespread generalized slow wave activity and a

FIG. 5. Variation in urine output in relationship to treatment given.

FIG. 6. Variation in urine osmolality in relationship to treatment given.

gammascan showed a high suprasellar uptake of isotope.

Other investigations at this stage showed a blood cholesterol of 125 mg/100 ml.; protein-bound iodine 2.7 μ g/100 ml.; and the T_3 resin uptake test 21.4%. Examination of the urine showed an excretion of 11.8 mg of total oestrogens per 24 hours (17.7 mg = 100%); 2.0 i.u. of follicular stimulating hormone per 24 hours and less than 10 i.u. of luteinizing hormone per 24 hours.

Within one week of admission the chest radiograph became clear and therefore antituberculous therapy was withdrawn. By this time she was fully conscious and able to give a history of one month's

transient polydipsia and of polyuria two months before admission.

Steroids were now withdrawn and a short synacthen test revealed a low resting cortisol level with a normal response. The resting cortisol level at 9.00 a.m. was 5.3 μ g/100 ml. After 1 mg synacthen subcutaneously the cortisol level was 20 μ g/100 ml. after 45 minutes and 23.2 μ g/100 ml. after 60 minutes.

Steroids were then reintroduced and pitressin was withdrawn for a trial period during which time she developed a high urinary output with resulting hypernatraemia and dehydration. Despite high serum osmolalities she did not become thirsty at any

FIG. 7. *Sagittal section of brain showing the tumour in the hypothalamus.*

FIG. 8. *Section of tumour showing two main cell types. Haematoxylin and eosin stain. $\times 535$.*

stage. Pitressin was therefore recommenced and fluid balance was restored.

Subsequently, steroids were again withdrawn and she became oliguric (700 ml. urine/day) with a high urinary osmolality 80 (mosm/l.) and low serum osmolality (257 mosm/l.).

Figures 3 to 6 show the variations in serum sodium

and osmolality and urine output and osmolality respectively in relationship to the treatment given.

At this stage a diagnosis of hypothalamic tumour was assumed and full replacement therapy with steroids, pitressin, and thyroxin was commenced. For a short period her general condition remained satisfactory with reasonable control of fluid and

electrolyte balance, though she was persistently hypothermic and her optic discs appeared progressively paler.

Before any definitive treatment could be considered, she lapsed into coma without disturbance of fluid balance and developed extensor spasms of the arms and flexor spasms of the legs. She died without regaining consciousness.

POST MORTEM EXAMINATION The body was that of an emaciated girl aged 22 years. The relevant gross findings were confined to the brain where there was a partially cystic greyish mass of tumour in the hypothalamus extending from the mamillary bodies posteriorly to the optic chiasma anteriorly. It involved the lamina terminalis and the anterior and medial thalamus (Fig. 7). The lungs showed bronchopneumonia.

Histologically, the tumour was composed of two cell types, one cell being small and round and very similar to a lymphocyte; the other type was considerably larger, with round nuclei and prominent nucleoli (Fig. 8). Mitotic figures were easily found. The cysts noted macroscopically were full of pale eosinophilic colloid. No other tissue components were seen in sections taken at multiple levels. The tumour appeared to be actively infiltrating the cerebral tissues at its edges and there was a mild gliotic reaction around it. The picture was that of an 'ectopic pinealoma' (germinoma or atypical teratoma).

CASE 2

A fresh sample of tumour was provided from a necropsy on a woman aged 19 years with an ectopic pinealoma by Dr. P. G. Lynch, Department of Neuropathology, Manchester University. Histologically the tumour showed features similar to the previous case.

METHODS

A sample of fresh testicular seminoma was obtained from a surgical specimen. Three normal adult pineal glands were obtained from necropsies performed within 12 hours of death. Blocks from all three tissues were frozen onto chunks with liquid nitrogen and cryostat sections were cut at 10 μ . The following histochemical staining reactions were performed:

DEHYDROGENASES The technique was that of Pearse (1960) using the following substrates: sodium L-glutamate, sodium DL- β -hydroxybutyrate, glucose-6-phosphate disodium salt, 6-phosphogluconic acid barium salt, sodium DL- α -glycerophosphate, sodium DL-isocitrate, sodium lactate, sodium succinate, and

sodium malate. A fresh solution of 0.1M triphosphopyridine nucleotide was used for the pentose-shunt enzymes, no coenzyme was used for succinic dehydrogenase, and 0.1M diphosphopyridine nucleotide was used for the rest. Sodium cyanide (0.1M) was used as a respiratory inhibitor for all enzymes except the pentose-shunt enzymes where 0.1 M sodium azide was used instead.

Sections were incubated for 45 minutes at 37° C.

DIAPHORASES Sections were incubated in a medium containing 0.1M reduced diphosphopyridine nucleotide (DPNH) or reduced triphosphopyridine nucleotide (TPNH) and nitroblue-tetrazolium at pH 7.4 for 45 minutes.

CYTOCHROME OXIDASE The method of Burstone (1960) using p-aminodiphenylamine and 3-amino-9-ethylcarbazole was used. Sections were incubated for one hour before chelation in cobaltous acetate.

ALKALINE PHOSPHATASE A naphthol AS-TR phosphate method was used (Burstone, 1958). The pH of the incubating medium was 8.9 and Red Violet L-B salt was used as coupling agent.

ACID PHOSPHATASE A similar method to that used for alkaline phosphatase was used except that the pH of the incubating medium was 5.2.

NON-SPECIFIC ESTERASE The method was based on Gomori's modification of the technique of Nachlas and Seligman (1949) using α -naphthyl acetate as substrate, and Fast Blue BB salt as coupling agent.

TABLE

ENZYMES FOUND IN DIFFERENT TISSUES EXAMINED

Enzyme	Pinealoma		Seminoma		Pineal gland	
	Large cells	Small cells	Large cells	Small cells	Pineocytes	Glia
Dehydrogenases						
6-phospho-gluconic acid	+	+	+	+	+	+
G-6-Phosphate	+	+	+	+	+	+
α -glycerophosphate	+	+	+	+	+	+
Lactic acid	+	+	+	+	+	+
Isocitric acid	+	+	+	+	+	+
Succinic acid	+	+	+	+	+	+
Malic acid	+	+	+	+	+	+
Glutamic acid	+	+	+	+	+	+
β -Hydroxy-butyric acid	+	+	+	+	+	+
DPNH diaphorase	+	+	+	+	+	+
TPNH diaphorase	+	+	+	+	+	+
Cytochrome oxidase	+	+	+	+	+	+
Acid phosphatase	+	+	+	+	+	+
Esterase	+	+	+	+	+	+
Leucine amino-peptidase	0	0	0	0	0	0
Alkaline phosphatase	+	—	+	—	—	—

FIG. 9. *Non-specific esterase stain on pinealoma showing strong activity in large cells and weak activity in small lymphocyte-like cells. $\times 540$.*

FIG. 10. *Non-specific esterase stain on seminoma showing strong staining of large cells and weak staining of lymphocytes. $\times 540$.*

FIG. 11. *Alkaline phosphatase stain on pinealoma showing strong staining of large cells and negative reaction in small cells. $\times 800$.*

FIG. 12. *Alkaline phosphatase stain on seminoma showing strong reaction in large cells and negative reaction in lymphocytes. $\times 540$.*

LEUCINE AMINOPEPTIDASE The method was that of Burstone and Folk (1956) using L-leucyl- β -naphthylamide as substrate. Sections were incubated for one hour at pH 7.1.

RESULTS

The Table shows the enzymes found in the various cell types. All enzymes investigated, with the exception of leucine aminopeptidase and alkaline phosphatase, were present in all cell types. The large cells of both the pinealoma and seminoma and the pineocytes showed stronger activity than the small round cells and glia (Figs 9 and 10). No cells showed leucine aminopeptidase activity.

The most striking and significant feature was the presence of strong alkaline phosphatase activity in the large cells of both the pinealoma and the seminoma (Figs 11 and 12). No activity was seen in pineocytes.

DISCUSSION

There has been a considerable amount of controversy as to the nature of the 'ectopic pinealoma'. They have been thought by some (Russell, 1954, Løken, 1957, Simson, Lampe, and Abell, 1968) to be closely related to the germinomas of the pineal gland, the seminoma of the testis, and the dysgerminoma of the ovary.

In an electron microscopical study Ramsey (1965) stated that this type of tumour shows no striking resemblance to epithelial cells, ependymal cells, or parenchymal cells of the pineal gland. Brihaye and Parmentier (1955) also felt that the lack of affinity for silver of the large cells was against their being derived from pineal parenchymal cells. We are unaware of any previous histochemical comparison between this type of tumour and a seminoma of the testis.

The histochemical finding of a virtually identical pattern in the ectopic pinealoma and the seminoma provides some further evidence that these two tumours are, in fact, closely related and that the term atypical teratoma is probably more appropriate than ectopic pinealoma. The most striking feature was the presence of strong alkaline phosphatase activity in the large cells of both tumour types. This enzyme was not seen in pineocytes of the normal pineal gland. The similarities between the other enzymes studied could occur by chance as they

are nearly all possessed to a certain degree by most cell types. Large cells would probably be expected to show a higher activity in view of the greater amount of cytoplasm. Alkaline phosphatase, however, is an uncommon enzyme and is related in most cases to specific function, usually to the transport of substances across membranes—that is, in capillaries, choroid plexus, arachnoid granulations, biliary epithelium, small intestinal epithelium, and the proximal renal convoluted tubule. It is unlikely that the finding of its activity in two histologically similar cells would be found by chance alone, certainly in view of the fact that no similar cell is seen in the normal pineal gland.

On the clinical side the first case showed several features of additional interest. It presented with a symptom complex which was confidently diagnosed and successfully treated as anorexia nervosa. The patient was a young female with a higher than average IQ who had become involved in the pursuit of thinness (Bruch, 1965; *British Medical Journal*, 1969). While Lewin, Mattingly, and Millis (1972) have described a case of anorexia nervosa due to a well differentiated astrocytoma, they were unable to explain the anorexia on anatomical grounds. As the tumour, unlike our case of ectopic pinealoma, was not involving the lateral hypothalamus where animal experiments have located the feeding centre (Anand and Brobeck, 1951).

The subsequent hospital presentation of our case in hypernatraemic coma raised various possibilities; these included hyperosmolar diabetic coma, diabetes insipidus, nephrogenic diabetes insipidus, intracranial disease, salt poisoning, or gastrointestinal fluid loss. The absence of any recent polyuria or polydipsia seemed to exclude a diagnosis of diabetes insipidus and other possibilities were not substantiated. It would seem likely that the hypernatraemic dehydration was explained by the development of hypodipsia due to destruction of the thirst centre in the anterior hypothalamus. This is a rare occurrence that has previously been described as occurring after subarachnoid haemorrhage (Jenkins, 1972).

The supportive administration of steroids when our patient was comatose resulted in gross polyuria due to unmasking of diabetes insipidus. It is known that cortisol is necessary for the

excretion of a water load and that integrity of adenophyseal function is necessary for the polyuria of diabetes insipidus. In our case, the anterior pituitary gland was shown to be histologically normal and we believe that its function was impaired as a result of destruction of the median eminence of the hypothalamus where releasing hormones, including corticotrophin releasing factor, are produced. As the posterior pituitary gland was also intact, the diabetes insipidus was presumably due to damage occurring at some level up to, or including, the supra-optic nucleus. It is not unusual to encounter transient symptoms of diabetes insipidus, as in our patient, when posterior pituitary function is first lost and cortisol production is subsequently impaired. Furthermore, corticosteroid administration in this situation will unmask diabetes insipidus (Kageyama, 1971).

There are a few reports of successful treatment of ectopic pinealoma by radiotherapy (Horrox and Wyatt, 1947; Troland and Brown, 1948; Rubin and Kramer, 1965; Kageyama, 1971). It is important, therefore, to recognize the possibility of ectopic pinealoma presenting in the manner of our patient.

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