Solitary choroidal metastasis from bronchial carcinoid

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Carcinoid tumours are low-grade adenocarcinomas which originate from Kulitschitzky cells of the enterochromaffin system. Although most frequently found in the gastrointestinal tract, carcinoid may arise from any enterochromaffin tissue. A common location of primary carcinoid is the lung; and about 10 per cent. of these carcinoids metastasize. There have been only two previous reports (Font, Kaufer, and Winstanley, 1966; Rosenbluth, Laval, and Weil, 1960) of carcinoid metastasizing to the choroid; both tumours originated in the lung. This paper reports a much more extensively documented third case of bronchial carcinoid metastatic to the choroid, with chest *x* rays, histopathology of the original lung tumour, fundus photography, fluorescein angiography, ultrasonography, radio-isotope data, electron microscopy, and gross and microscopical photographs of the choroidal tumour.

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FIG. 1(a) *Postero-anterior chest x ray taken in September, 1970, showing lobulated lemon-sized right hilar mass*

Case report

A 29-year-old white woman had been in good health until September, 1970, when she developed a dry, non-productive cough and a low-grade fever. A chest *x* ray showed a lobulated right hilar mass (Fig. 1a, b), initially thought to be suggestive of Hodgkin's disease or sarcoidosis. The findings on general physical examination and the laboratory data, including haemogram, urine analysis, liver function tests, and serum protein electrophoresis, were within normal limits. Frozen sections of bilateral scalene node biopsies failed to reveal any abnormality. However, upon right anterior thoracotomy, a multilobulated lemon-sized tumour was found in the right hilum. A bi-lobectomy of the two lower lobes of the right lung was done. Frozen sections showed the tumour to be a bronchial carcinoid; histopathological sections indicated that the tumour was completely excised. Tumour cells were found, however, in one hilar lymph node (Fig. 2), and special stains revealed them to be argyrophilic.

The patient remained asymptomatic until December, 1972, when she noted the onset of "flashbulb-like sensations" in the left eye lasting for several seconds and recurring four or five times a day. Although she denied any complaints suggestive of systematic carcinoid and other significant symptomatology, she was investigated in February, 1973, for recurrence of the tumour or metastases.

FIG. 1(b) *Lateral view, showing mass*

FIG. 2 Photomicrograph of section through primary tumour, showing cord-like arrangement of cells, plump nuclei, and multiple fine nucleoli typical of carcinoid. Haematoxylin and eosin. $\times 320$

Examination

This was unremarkable except for the ocular findings. The uncorrected visual acuity was 20/20 in each eye, and refraction showed her to be essentially emmetropic. Findings on external examination were entirely within normal limits, as were slit-lamp examination, ocular tensions by applanation, and gonioscopy. Ophthalmoscopy of the right eye was unremarkable; however, in the left there was a sharply demarcated, 4 disc diameter, dome-shaped, whitish-

FIG. 3 Fundus photograph of left eye, showing choroidal mass with overlying retinal detachment

yellow lesion temporal to the fovea, with an overlying serous detachment of the neurosensory retina (Fig. 3).

Central and peripheral fields of the right eye were full on Goldmann and tangent screen perimetry. In the left eye central field examination showed a sloping nasal defect, and peripheral field examination demonstrated a 5 disc diameter dense nasal scotoma corresponding to the lesion. Radio-isotopic scanning utilizing P^{32} resulted in statistically significant higher counts in the left eye at both 24 and 48 hrs. Fluorescein angiography demonstrated a 4 disc diameter raised oval lesion which blocked fluorescence centrally but was bordered by a ring of hyperfluorescence, thickest inferotemporally (Fig. 4a, b). In the later stages of the angiogram the mass stained diffusely. An overlying detachment of the neurosensory retina was evident. Ultrasonography showed a mass with a base 7 mm in diameter, elevated $4\frac{1}{2}$ mm. The lesion was acoustically solid and failed to show evidence of choroidal excavation, as is usually seen with a melanoma. The retrobulbar echo pattern was interpreted as normal. Hence, the clinical appearance as well as the radio-isotopic scanning, fluorescein angiography, and ultrasonography data were consistent with either choroidal melanoma or a metastatic choroidal lesion, probably carcinoid.

Normal laboratory studies included haemogram, electrolytes, serum calcium, serum phosphorus, serum iron, iron binding capacity, VDRL, urine analysis, Pap smear, liver function tests, thyroid function tests, fasting blood sugar, chest x ray, bone scan, brain scan, liver scan, spleen scan, and 24-hour urinary 5-hydroxylin-dolacetic acid.

Progress

During the next 4 weeks the symptoms of retinal detachment became more frequent. The best corrected visual

FIG. 4 *Fluorescein angiograms demonstrating blocked fluorescence centrally with ring of hyperfluorescence (a) with subsequent diffuse staining of the mass (b)*
(a) arteriole phase (10–12 sec.)

acuity in the left eye had deteriorated to 20/50, the neurosensory detachment had extended closer to the macula, and the underlying mass appeared larger. Diagnosis of both choroidal melanoma and carcinoid were considered.

Operation

Enucleation was carried out.

(b) late staining (30 min.)

Result

At the time of this report 3 years have elapsed since removal of the primary tumour and 15 months since enucleation, and the patient remains asymptomatic.

HISTOPATHOLOGICAL FINDINGS

Gross examination

After enucleation the globe was fixed immediately in phosphate-buffered 5 per cent. glutaraldehyde at 4°C. for 1 hr. An area of decreased transillumination was present temporal to the optic nerve. A 2 × 3 × 2 mm. elevated, pearly-white choroidal tumour was noted temporal to the

FIG. 5a, b *Photographs of sectioned globe revealing white choroidal tumour temporal to optic nerve. ×2.5*

optic nerve; the surrounding retina was slightly detached (Fig. 5*a, b*). The remainder of the findings on gross examination were within normal limits.

A 1 mm. thick slice of tissue through the tumour was postfixed in phosphate-buffered osmium tetroxide and processed for electron microscopic examination.

Light microscopy

The cornea, anterior chamber, angle, iris, ciliary body, lens, vitreous, optic nerve, and sclera were normal. A large, unencapsulated, well-circumscribed tumour was present in the posterior choroid, temporal to the macula. The tumour was composed of uniform cells, round to oval in shape, containing a moderate amount of pink cytoplasm

with well-defined cellular outlines. The tumour cells contained plump nuclei and multiple fine nucleoli; rare mitotic figures were present. The cells were arranged in cords and ribbons, groups occasionally forming tubular structures; many vascularized fibrous septa were present. In some areas the tumour had dissected into the superficial sclera and in other areas it appeared to compress the posterior choroid. Blood vessels temporal and nasal to the tumour were engorged and the choroid appeared oedematous. The retinal pigment epithelium (RPE) appeared necrotic with loss of cells nasally and temporally. There was in addition marked fibrous metaplasia of the RPE overlying the tumour. In areas between the RPE and neural retina chronic inflammatory cells were noted. The

FIG. 6(*a*) *Medium-power microscopic view of tumour, showing necrosis of retinal pigment epithelium nasally and temporally and its marked metaplasia overlying the tumour. There is cystoid degeneration and serous detachment of the neural retina* $\times 42$.

FIG. 6(*b*) *High-power view of tumour cells, showing well-vascularized arrangements of cords and tubular structures.* $\times 260$

neural retina overlying the tumour had undergone severe cystoid degeneration with prominent loss of the photoreceptor and ganglion cells. A serous detachment of the neural retina surrounding the tumour was present (Fig. 6a, b). In the area between the disc and the tumour the internal limiting membrane was severely wrinkled with underlying cystic spaces containing amorphous material. Silver staining by the Fontana-Masson method was positive for argentophilia.

The pathological diagnoses were bronchial carcinoid metastatic to the choroid with a secondary serous retinal detachment.

Electron microscopy

Some of the ultrastructural findings were similar to previous descriptions of carcinoid tumours (Bensch, Gordon, and Miller, 1965a; Black, 1968; Gmelich, Bensch, and Liebow, 1967; Luse and Lacy, 1960; Toker, 1966). In contrast to the uniform staining appearance of the tumour cells at the light microscopic level, electron microscopy demonstrated light and dark cell types (Fig. 7). There was a large nucleus to cytoplasm ratio. The nuclei of both cell types were round to ovoid and contained coarsely clumped chromatin adjacent to the nuclear envelope. Large nucleoli were prominent and occasional cells contained two nuclei. The scant cytoplasm contained abundant rough endoplasmic reticulum. Small, round mitochondria appeared throughout the cytoplasm, but several areas of tightly packed mitochondria suggested polarization of some of the tumour cells. Also present throughout the cytoplasm, and occasionally in clusters around the cell periphery, were characteristic neurosecretory granules. These granules were bounded by a unit membrane and consisted of an electron dense core surrounded by an electron lucent zone (Fig. 8). The Golgi apparatus was not prominent. The

cytoplasm of many cells contained distinct, finely dispersed fibrils. There were few interdigitations of plasma membranes of adjacent tumour cells. However, numerous intercellular spaces and channels with projecting microvilli coursed between cells (Fig. 9a). In some areas these channels widened to form a gland-like structure; here the microvilli were arranged in an orderly fashion (Fig. 9b). The lumen of these "glands" contained dense fibrils and occasional free neurosecretory granules. No granules were observed in the capillary endothelial cells of the connective tissue stroma.

Discussion

Bronchial adenomas were first described histologically by Müller (1882). Kramer (1930) first used the term "bronchial adenoma" to distinguish a type of tumour which was more benign, in behaviour and morphology, than bronchogenic carcinomas. Hamperl (1937) subsequently subdivided bronchial adenomas into two groups, the most common of which he felt resembled intestinal carcinoid. The other group he described as cylindromas because of their resemblance to salivary gland tumours. These classifications are still used, although a third type, "mucoepidermoid", has been added. For some time there was great disagreement whether the carcinoid-resembling tumours of the lung were related to the carcinoid tumours of the gastrointestinal tract. The main reason why these tumours were thought to be unrelated was that there were histological differences, notably a lack of argentaffinity in the bronchial carcinoid. Also, the carcinoid syndrome, first described in depth by Thorson, Björck, Björckman, and Waldenström (1954),

FIG. 7 Electron micrograph of typical light and dark cell types. Note cell containing two nuclei. $\times 37,000$

FIG. 8 *Ultrastructure of neurosecretory granules. An electron dense core bounded by a unit membrane is evident in the granules shown here (some in a cluster) at the cell periphery. $\times 42,000$*

FIG. 9(a) *Electron micrograph, showing intercellular channels widening into an intercellular space into which microvilli project. $\times 30,000$*

FIG. 9(b) *Another widening of an intercellular channel forms a gland-like structure containing an orderly array of microvilli. Here the lumen contains dense fibrils. $\times 11,250$*

was found initially only in association with malignant carcinoid tumours of the gastrointestinal tract, and it was not until 1956 that the first cases of carcinoid syndrome associated with bronchial carcinoid were reported (Kincaid-Smith and Brossy, 1956). It is now generally accepted that carcinoid tumours arise from Kultschitzky cells of the enterochromaffin system. Recent electron microscopical studies (Bensch, Gordon, and Miller, 1965b; Bensch, Corrin, Pariente, and Spencer, 1968; Gmelich and others, 1967) have demonstrated Kultschitzky-type cells in bronchial epithelium wedged between the basal parts of the columnar epithelium which lines the bronchial ducts and glands.

In various series (Donahue, Weichert, and Ochsner, 1968; Ochsner, Seymour, and Ochsner, 1957; Toole and Stern, 1972; Turnbull, Huvos, Goodner, and Beattie, 1972), bronchial adenomas were found to comprise from 1 to 10 per cent. of all primary pulmonary tumours. Carcinoid accounts for 80 to 85 per cent. of these bronchial adenomas, and cylindromas about 12 to 15 per cent. (Batson, Gale, and Hickey, 1966; Goodner, Berg, and Watson, 1961; O'Grady, McDivitt, Holman, and Moore, 1970; Toole and Stern, 1972; Turnbull and others, 1972; Wilkins, Darling, Soutter, and Sniffen, 1963). In general about 10 per cent. of bronchial adenomas have metastases (McBurney, Kirklin, and Woolner, 1953), although in one study (Goodner and others, 1961) 44 per cent. of the patients had metastases at the time of operation. With carcinoid, the incidence of metastases appears to be related to the type and histology (O'Grady and others, 1970; Pearson and Fitzgerald, 1949; Turnbull and others, 1972; Wilkins and others, 1963), the degree of anaplasia (Arrigoni, Woolner, and Bernatz, 1972; Bensch and others, 1968; Goodner and others, 1961; McBurney and others, 1953), and the size of the primary tumour (Barclay and Robb, 1968; Moertel, Sauer, Dockerty, and Baggenstoss, 1961; Teitelbaum, 1972). Cylindromas metastasize three times as frequently as carcinoid (McBurney and others, 1953). Several studies of patients with carcinoid tumours of the gastrointestinal tract have found a high frequency, 25 to 40 per cent. of a second primary tumour (Kuiper, Gracie, and Pollard, 1970; Martin, 1970; Moertel and others, 1961; Pearson and Fitzgerald, 1949; Teitelbaum, 1972). This finding has not yet been confirmed for bronchial adenomas.

Treatment

As with most malignant neoplasms, the treatment of choice for carcinoid is wide resection of the primary growth with removal of local lymph nodes and any accessible metastases (Bargen, 1961; Batson and others, 1966; Brindley and Bonnet, 1967; Davies, 1959; Ochsner and others, 1957; O'Grady and others, 1970; Overholt, Bougas, and Morse, 1957; Pearson and Fitzgerald, 1949; Smith, 1969; Teitelbaum, 1972;

Weisel, Lepley, and Watson, 1961; Wilkins and others, 1963). It is significant that, for patients receiving this treatment a relatively good prognosis has been reported (Batson and others, 1966; O'Grady and others, 1970; Overholt and others, 1957; Wilkins and others, 1963). Chemotherapy is generally reserved for patients with widespread, inoperable metastases or with carcinoid syndrome, which most frequently develops after the primary tumour has metastasized to the liver (Bargen, 1961; Hill, 1971; Oates and Butler, 1967). In the latter case therapy usually consists of hormonal antagonists or symptomatic treatment of the diarrhoea, pain, dizziness, and oedema which usually accompany carcinoid syndrome. Hill (1971) has reviewed the specific pharmacological approaches to the treatment of carcinoid syndrome.

Reed, Kuipers, Vaitekevicius, Clark, Drake, and Eyler (1963) had some success with antineoplastic agents (alkylating agents and antimetabolites) given by hepatic artery infusion. Chemotherapy was not indicated in our patient because her lesion was surgically accessible and she had no manifestations of carcinoid syndrome or evidence of any other metastases.

Malignant melanomas of the choroid have been treated experimentally (Burns, Allen, and Fraunfelder, 1969) and clinically (Stallard, 1966) by irradiation of the lesion. However, preoperatively it was considered more probable that the tumour in our patient was a metastatic carcinoid which is generally considered to be radioresistant (Bargen, 1961; Brindley and Bonnet, 1967; Davies, 1959; Goodner and others, 1961; Holsti, 1967; Reed and others, 1963; Wilkins and others, 1963). In certain instances high voltage doses have been used on skin metastases with some regression of the tumour. However, in most cases of carcinoid, the results obtained with irradiation have been disappointing, and there is no good evidence that radiotherapy is of any value, other than for possible palliation of bone pain (Martin, 1970). In our case, the high doses of irradiation considered necessary by the radiotherapists carried the risks of destruction of the eye and post-radiation sarcoma (Soloway, 1966; Steiner, 1965). Although the possibility of local excision of tumours in the posterior segment of the choroid has recently been reported (Peyman, Nelsen, Axelrod, Graham, and Daily, 1973), this technique is still regarded as experimental; and in our patient the tumour was located so near to the macula that useful vision could probably not have been salvaged by excision. Enucleation was chosen because it offered the best long-term prognosis for this patient.

Summary

This report describes the clinical, light microscopical, and electron microscopical features of a metastasis from a bronchial carcinoid tumour occurring in a

29-year-old white woman. The eye lesions was diagnosed 30 months after resection of the primary pulmonary tumour. Ophthalmoscopically the patient was observed to have a solid choroidal mass. Enucleation was carried out because of the possibility that the tumour was a primary choroidal melanoma. Enucleation was also indicated because of the relatively good prognosis for long-term survival in patients following excision of metastases from a bronchial carcinoid tumour. By light microscopy the

metastasis was seen to be composed of cords; and ribbons of cells which showed positive staining characteristics for argentophilia. On electron microscopical study, neurosecretory vesicles, numerous microvilli, mitochondria, and light and dark cells, characteristic of endocrine tissue in different states of activity were noted.

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