Retretion in testicular seminoma with viable metastases

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SYNOPSIS Stages in the retrogression of testicular seminoma are described. Eosinophilic necrosis fringed by palisaded histiocytes may be followed by fibrous replacement. Oxidation of unsaturated phospholipids in necrotic tumour may lead to deposition of lipofuscin around the lesion. Search for partially or completely scarred lesions is essential before contemplating a diagnosis of primary retroperitoneal seminoma.

Retrogressed seminoma can often be distinguished from retrogressed teratoid tumours. Apparently paradoxical teratoid metastases in association with a testicular seminoma are explained on the basis of misinterpreted retrogressed teratoid tumours in association with the seminoma.

Inguinal node metastases from testicular seminoma may be the result of abnormal lymphatic drainage following previous scrotal operations, testicular torsion etc.

Testicular scars representing a fibrosed source of origin of extragenital choriocarcinoma and other teratomatous metastases have been recognized since Prym's (1927) description. Stowell, Sachs, and Russell (1945), however, when reporting one of the most thoroughly documented instances of primary extragenital choriocarcinoma, disputed the significance of these testicular scars, and Lynch and Blewett (1953) went so far as to suggest that the scars themselves might be the consequence of primary extragenital growths. The speculative view of the latter workers has been quoted by others (e.g., Ainsworth and Gresham, 1960). Azzopardi, Mostofi, and Theiss (1961), on the basis of 17 cases in the files of the Armed Forces Institute of Pathology, Washington, D.C., strongly supported the contention that testicular scars can represent sites of fibrosed primary gonadal tumours and drew attention to the significance of haematoxyphil deposits in the seminiferous tubules in retrogressed testicular teratoid neoplasms. They cautioned against an uncritical acceptance of cases of allegedly primary extragenital, and especially retroperitoneal, embryonal carcinoma and choriocarcinoma. That retrogression with scarring occurs also in testicular seminoma is not generally appreciated.

The purpose of this paper is to report a case illustrating the pattern of regression in a testicular seminoma accompanied by viable metastases and to discuss the implications of these findings.

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fast bacilli were seen in the urine and no tubercle bacilli found on culture. A chest radiograph was normal, as was an E.C.G.

The patient was treated with bed rest, anticoagulants, and antibiotics; the pain and swelling in the leg diminished. On 20 August an excision biopsy of an inguinal lymph node was carried out and, as the left cord was thickened and hard, a left orchidectomy was performed with removal of the spermatic cord. He made a good post-operative recovery and was discharged on 30 August. On 16 September the left leg was found to be swollen again and the left inguinal nodes were palpable. In view of the pathological findings (see below) he was given a course of radiotherapy on a Cobalt machine, treating the left groin and iliac fossa with an incident dose of 6,000 r over 24 days; the lumbar region received an incident dose of 3,600 r through an anterior field over the same period. When seen on 21 December 1963 he had improved and was feeling well.

PATHOLOGY

INGUINAL LYMPH NODE This was received in two fragments, the larger measuring 2·5 × 1·5 × 1·0 cm. The node is largely replaced by metastatic seminoma (Figs. 1 and 2). There is a histiocytic granulomatous reaction in the stroma of the type frequently associated with seminoma. Staining with Best's carmine reveals abundant glycogen in the tumour cells, a feature of the classical variety of seminoma.

ORCHIDECTOMY SPECIMEN This consists of the left testis, 4 × 2·5 × 2·5 cm., and the spermatic cord, 6 × 1·5 × 1·0 cm. There is fibrous thickening of the tunica vaginalis. On section the testis is firm, fibrous and white. On its posterior aspect, slightly to one side of the rete, there is a group of circular, yellow amorphous areas up to 0·5 cm. diameter and together involving an area 1·4 × 0·8 cm. On serial section of this zone it measures 2 to 3 mm. in depth.

Numerous blocks show fibrosis and hyalinization of the testicular parenchyma with only occasional, barely visible ghosts of seminiferous tubules. The epididymis shows slight tubular atrophy and moderate interstitial fibrosis with occasional lymphoid foci; it is firmly bound to the testis. The caput is relatively well preserved as is the appendix epididymis. There is dense fibrosis around the vas deferens.

The most significant findings are in the block containing the yellow amorphous foci. In addition to fibrosis this contains irregular areas of eosinophilic necrotic tissue (Fig. 3): these foci vary in number from two to six at different levels. On closer inspection each focus is found to consist of closely aggregated, large, rounded, degenerate tumour cells which have lost their nuclear staining, a feature commonly

FIG. 1. Metastatic seminoma in lymph node with histiocytic stromal reaction best seen at the top. Haemalum and eosin × 120.

FIG. 2. Higher magnification of tumour cells in lymph node. Large nucleoli and a punctate chromatin pattern are visible. Haemalum and eosin × 750.
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FIG. 3. Foci of eosinophilic necrotic tissue containing clefts of cholesterol esters. Calcification has resulted in the artefactual line across the photograph. Haemalum and eosin × 38.

FIG. 4. Edge of necrotic focus showing outlines of individual degenerate tumour cells. Masson trichrome × 370.

FIG. 5. Palisade of histiocytes and fibroblasts at edge of necrotic seminoma. Heidenhain's azocarmine × 100.
seen in the necrotic areas of seminoma. The obscured
cytological details are rendered a little clearer by
staining with Masson's trichrome (Fig. 4). Serial
sections, staining every fourth slide, show no
evidence of viable seminoma. The necrotic foci
have sharp edges and are ringed by a layer of
histiocytes and fibroblasts which tend to a perpen-
dicular orientation (Fig. 5), the whole appearance at
a low magnification bearing a superficial resembl-
ge to a subcutaneous rheumatoid nodule (Fig. 3).
Occasional foamy macrophages, lymphocytes, and
a few plasma cells complete the composition of the
cellular infiltrate. Many of the arteries around the
necrotic foci show marked intimal fibrous thickening.

In paraffin sections, the necrotic tissue stains
moderately deeply with Sudan black B and is
negative with P.A.S.: this indicates its phospholipid
content. Since a small amount of phospholipid is
present in the viable metastatic seminoma, the
phospholipid at the site of the primary tumour may
represent a concentration of intrinsic phospholipid
by removal of protein, glycogen, and other more
soluble constituents. It is not possible, however, to
exclude the addition of phospholipid to the necrotic
material from extraneous sources.

Haematoxyphilic deposits are present in large
masses in the centre and in smaller aggregates at the
edges of the necrotic foci. The Feulgen reaction is
negative; the absence of deoxyribonucleic acid is not
surprising in view of the ease with which it appears
to be removed from necrotic seminomatous tissue.
Calcium carbonate or phosphate is present in the
haematoxyphilic deposits as demonstrated by
napthochrome green B and Von Kossa; these stains
also show a fine sprinkling of calcium salts in the
necrotic tissue as a whole. A haematoxyphilic
reaction has often been erroneously attributed to
calcium salts when it is in fact caused by substances
laid down before or together with calcium (Azzo-
pardi, 1959). In the present case large amounts of
mucopolysaccharide are present in the haematoxy-
philic deposits as shown by Southgate mucicarmine
and by Alcian green, provided nuclear counterstains
are omitted in both methods so as not to obscure
the red or green staining. A small amount of
greenish-yellow pigment, probably haematoxid, is
present in one necrotic zone.

The histiocytes bordering the necrotic foci (Fig. 6)
give a strongly positive Sudan black reaction and a
positive P.A.S. reaction. On close inspection of the
haemalum-eosin sections, these cells are found to
contain a finely granular, pale yellow pigment. This
contains no stainable iron and the suspicion that it
might be lipofuscin is confirmed by the golden-
yellow autofluorescence in ultra-violet light. The
pigment is also acid-fast and identifiable as lipo-

FIG. 6. Histiocytes containing finely granular lipofuscin.
Haemalum and eosin \times 370.

duscin of ceroid type. A very small amount of
haemosiderin is present in histiocytes adjacent to one
of the necrotic foci.

DISCUSSION

This case illustrates the stages in the regression of a
primary testicular seminoma. Necrosis of tumour
results in accumulations of ghosts of neoplastic cells
in which cytological detail is lost and specific nuclear
staining no longer possible. The degenerated
tissue excites a histiocytic reaction at the periphery.
Cholesterol and its esters may appear in the necrotic
tumour and foam cells may be seen in the peripheral
reactive zone. More important is the presence of
phospholipid in the necrotic tumour; auto-oxidation
of unsaturated fatty acids of phospholipids leads to
the appearance of a lipofuscin pigment, of ceroid
type, in the histiocytes fringing the necrosis. In the
absence of specific staining, this pigment is easily
mistaken for haemosiderin. Beyond the histiocytic
zone there is a band of dense fibrosis. In some
instances, possibly because of the large quantity of
necrotic tissue and its high fat content, necrotic
tumour may remain for long periods of time and become calcified. In other cases necrotic tumour may be completely removed with loss of the more specific features and replacement by a fibrous scar of variable size. In the case reported here, it is possible that the episode of probable testicular torsion suffered by the patient at an earlier date may have been an important factor in precipitating tumour necrosis. It must, however, be stressed that torsion is by no means an essential prelude to regression of testicular seminoma. In other cases seen by one of us and summarized in Table I, there was no indication of torsion in the clinical histories and in these patients the scarring and necrosis did not involve the entire testis but was limited to a part of the gonad. While radiotherapy might possibly have contributed to the scarring of the testicular lesions in some of these patients, it certainly was not responsible in cases 4 and 6 who had palliative treatment only.

Because of these findings, great caution is necessary before making a diagnosis of primary

### Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr.)</th>
<th>Clinical Presentation and Findings</th>
<th>Operative or Necropsy Findings, Progress and Therapy</th>
<th>Macroscopic Findings in Testis</th>
<th>Histology of Testis and Metastases</th>
<th>Additional Data and Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>Pain left flank with radiation to groin and testis. I.V.P. showed gross L. hydronephrosis</td>
<td>Massive retroperitoneal node involvement; L. nephrectomy and nodal excision; radiotherapy.</td>
<td>Large dense scar affecting about 2/3 of cut surface. Specimen step-sectioned</td>
<td>(a) No special features in testis scar (b) Seminoma in lymph nodes and peri-ureteric tissue</td>
<td>Histiocytic reaction in metastatic seminoma</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>Epigastric mass</td>
<td>Biopsy: seminoma. Radiotherapy to retroperitoneal mass; indurated area L. testis 3 months later; orchidectomy</td>
<td>Scar, 2 cm. max. diam., involving mediastinum</td>
<td></td>
<td>(a) At one end of scar, necrotic focus with acicular clefs, palisaded by foamy histo-zytes. Pigmented histiocytes + Some calcification (b) Seminoma in lymph nodes</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>Back pain, loss of weight, painless mass central abdomen, enlarged Virchow lymph node</td>
<td>Biopsy node: seminoma. Fibrous nodule, 0.3 cm. diam., near mediastinum L. testis</td>
<td></td>
<td>(a) No special features in testis scar (b) Seminoma in metastases</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>Low back pain, L. lower quadrant abdominal pain, fever, cough, loss of weight. Chest radiograph: bilateral lung metastases</td>
<td>Necropsy: metastases in para-aortic nodes, lungs, liver, pericardium</td>
<td>Wedge of firm white tissue, 2 x 2 cm., in L. testis, equidistant between the 2 poles and subcapsular in position</td>
<td>(a) Densely localized scar. Pigmented histiocytes +. In one section, minute focus of intratubular seminoma with some extratubular tumour cells. 'G' cells + + + (b) Seminoma with abundant necrosis in metastases</td>
<td>Only palliative therapy</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>Anorexia and weight loss, visible swelling in L. upper abdominal quadrant</td>
<td>Nitrogen mustard therapy. Necropsy: mass in region of duodenum, para-aortic and hepatic metastases</td>
<td>L. testis mostly fibrous with a small residue of recognizable parenchyma</td>
<td>(a) Densely fibrous, poorly defined scar, 'G' cells + (b) Seminoma in metastases</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Unknown</td>
<td>Anorexia and weight loss, low back pain, swelling L. neck, hard mass to R. of umbilicus, mass in R. inguinal region. Chest radiograph: mediastinal mass</td>
<td>Necropsy: metastases lungs, liver, nodes, etc.</td>
<td>Ill-circumscribed greyish mass replacing upper 2/3 of R. testis and merging with residual parenchyma</td>
<td>(a) Dense fibrous scar. Necrotic focus with 'ghost' cells, acicular clefs and some D.N.A. debris. Pigmented histiocytes + (b) Seminoma in metastases</td>
<td>Only palliative therapy</td>
</tr>
</tbody>
</table>

'G' cells is an abbreviation for the altered hyperchromatic germ cells, probably spermatogonia, found within seminiferous tubules and possibly representing the earliest seminoma in situ. They are more fully described in the paper by Azzopardi et al. (1961).
chorioncarcinoma (Azzopardi et al., 1961). This is not to be taken as implying that primary extragenital chorioncarcinoma in the male does not occur, since there are several well-documented accounts of primary tumours of this nature arising in the mediastinum (Laipply and Shipley, 1945; Lynch and Blewett, 1953) and in the pineal region. Seminoma may also originate in the anterior mediastinum.

The testicular lesion in this case illustrates the difference between regression and healing of seminoma and regression in the teratoid group of tumours. Thirteen of 17 teratoid tumours of the testis (Azzopardi et al., 1961) contained haematoxyphil deposits in the scar tissue; these formed sharply circumscribed foci because of their localization within seminiferous tubules and were characterized by their high D.N.A. content (Fig. 7). Necrosis in seminoma is mainly a feature of extratubular tumour and discrete haematoxyphil deposits are not seen. Previous authors have drawn no distinction between retrogression in seminoma and in the teratoid neoplasms of the testis. If only a fibrous scar is present in the testis, the nature of the primary tumour can only be surmised from the character of the metastases. In the presence of intratubular haematoxyphil deposits, one is justified in diagnosing a retrogressed teratoid tumour. Ghost neoplastic cells ringed by palisaded histiocytes sometimes containing lipofuscin are characteristic of the pattern of regression in seminoma, but this appearance is not specific and can be seen occasionally in other tumours. Nevertheless, where the testis contains conglomerates of 'shadow cells' associated with a histiocytic reaction we can, in the presence of seminomatous metastases, fairly assume the existence of a primary testicular seminoma. This view is supported by the present case report, by the other cases (Table I) one of us has had the opportunity of studying, and by analysis of a few cases in the literature. Quenu's (1960) patient had a fibrosed primary seminoma and cases 2 and 3 of Rather, Gardiner, and Frerichs (1954) are probably of this nature. Friedman (1951) recognized the occurrence of healing in testicular tumours. His Figs. 18 and 19, showing necrosis and sclerosis in an unspecified type of testicular tumour, very probably represent a seminoma: there is even a suggestion of palisaded histiocytes around the lesion.

The distinction between the two forms of regression has important applications and leads us to disagree with one of Friedman's fundamental conclusions. Friedman believes that the seminoma is the precursor of the embryonal carcinoma. His main evidence is that embryonal carcinomatous and chorionepitheliomatous metastases may appear when the primary testicular tumour is a 'germinoma', i.e., seminoma. Four germinomas with non-germinomatous metastases studied by the multiple-block method were found by Friedman to be pure germinomas, a finding which might tempt one to the conclusion he draws. However, if one studies his Fig. 22 it shows a good example of a seminoma alongside a regressed teratoma and it is lesions of the latter type that are responsible for the apparently paradoxical character of the metastases. The recognition of differences between the two types of regressed testicular tumour has histogenetic implications since it removes one of the main planks for the erroneous belief that seminoma may show transition to the teratomatous group of tumours.

A point of surgical interest in this patient, not related to the main theme, is the unusual development of and presentation with inguinal metastases.
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REFERENCES


from a testicular seminoma. Bowles (1962) has suggested that where there has been a previous scrotal operation, e.g., on a varicocele, or orchiopexy, a testicular tumour may metastasize to inguinal nodes because of alterations in the lymphatic drainage. Witus, Sloss, and Valk (1959) reported on two patients with testicular tumours developing after orchiopexy that metastasized to inguinal nodes and did not involve the retroperitoneal nodes. In the case reported here, there was an episode of probable torsion two years before the last hospital admission. Whatever the precise nature of this episode may have been, at orchidectomy the tunica vaginalis was partly obliterated by firm adhesions; this may well have resulted in variations in the normal drainage mechanism that led to the development of inguinal metastases. This case offers some support for Bowles' view of the circumstances in which testicular seminoma may involve the inguinal before the lumbar nodes. This hypothesis needs confirmation on a large series of testicular tumours.