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Physiological activity in mediastinal teratomata

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Sommerlad, B. C., Cleland, W. P., and Yong, N. K. (1975). *Thorax*, **30**, 510–515. **Physiological activity in mediastinal teratomata.** The clinical details of two patients with benign mediastinal teratomata are presented. Both patients developed inflammation of the root of the neck, the first after a small dose of radiotherapy and the second after a larger dose of radiotherapy and exploration of the thoracic inlet. In both cases, exploration of the inflamed area was followed by persistent discharge of fluid which was sterile on culture. In the first case, this was found to have a high cholesterol, lipid, and amylase content. In both cases, a benign mixed teratoma, with contents including intestinal epithelium and pancreatic tissue, was removed at thoracotomy. The suggestion is made that leakage of digestive enzymes from pancreatic, intestinal or salivary tissue may be a cause of inflammation in and around teratomata, especially after surgical exploration. Early thoracotomy is advised when the condition is recognized.

Mediastinal teratomata either cause no symptoms, being found on routine chest radiography, or cause symptoms such as wheezing or dysphagia by pressure on adjacent structures. Less commonly they become infected, sometimes after developing fistulous communications with the tracheobronchial tree, and they may occasionally present as an empyema. Malignant transformation has also been described. However, non-infective inflammation of tissues surrounding a teratoma has been less well documented. Two cases in which this occurred are described.

The constituent tissues of a teratoma may perform their normal physiological function. Examples reported to date include hair and tooth growth, sebaceous secretion, production of thyroid hormone (by an ovarian teratoma), secretion of chorionic gonadotrophin, and secretion of insulin. Exocrine secretion by pancreatic tissue has not previously been described.

CASE 1

A 22-year-old Caucasian girl was admitted to hospital in September 1950, two weeks after a routine chest radiograph had shown a lesion in the left superior mediastinum. She had no symptoms before the radiograph but afterwards felt some pain in the left scapular region and noted pulsation above the left breast. A repeat film one week after the first showed a marked increase in the size of the lesion. She had been delivered of a normal male infant two months before admission following medical induction of labour for post-maturity and hypertension. Routine chest films during the previous five years had been reported as normal. Her sister had had tuberculosis.

On examination after admission, pulsation was visible and palpable in the second left intercostal space. The chest film showed a lobulated mass in the superior mediastinum. The mass was seen to pulsate on screening but it was uncertain if this was intrinsic or transmitted. A full blood count was normal with a white cell count of 8000/mm^3. The Mantoux test was negative and plasma proteins normal (total 7·9 g/dl, albumin 4·6, globulin 3·3). A barium swallow showed no displacement or compression of either the oesophagus or trachea. Gynaecological examination showed no abnormality and no evidence of a chorioncarcinoma. A bone marrow biopsy showed a hyperplastic marrow but no abnormal cells. A provisional diagnosis of a reticulosis was made and a therapeutic test of radiotherapy (400 rads over three days) was carried out. However, the mass continued to increase in size. Over the next 11 days the patient complained of further pain, nausea, and vomiting and was intermittently

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pyrexial; two weeks after admission (eight days after completion of radiotherapy) she complained of pain in the root of the neck with dysphagia. A warm, tender swelling obliterated the suprasternal notch. Examination of a blood film showed a white cell count of 16 000/mm³ (polymorphs 14 560). Over the next two days the swelling extended to the right sternomastoid region. Attempted aspiration was unsuccessful.

Because the most likely diagnosis was still considered to be a reticulosis and in order to avoid an unnecessary thoracotomy, the neck swelling was explored through a transverse neck incision. Beneath the sternomastoid muscle the tissues were found to be oedematous and matted together. A small collection of fluid was found near the carotid sheath. No further fluid was found by finger dissection towards the thoracic inlet. A small drain was inserted. No pus cells, acid-fast bacilli or other bacteria were seen on examination of the fluid, which was sterile on culture. No evidence of neoplasm or inflammation was seen on microscopic examination of a small biopsy.

Copious clear discharge continued from a sinus in the wound, and the surrounding skin became acutely inflamed. The fluid was found on microscopy to contain many degenerate polymorphs, some cells resembling degenerate squamous epithelium, doubly refractile particles, and crystals. The pH was about 8·0. Biochemical examination showed a cholesterol content of 42–54 mg/dl, lipid content 430 mg/dl, amylase 8000 Somogyi units/dl, glucose 10 mg/dl, protein 0·8 g/dl, and chlorides 654 mg/dl as sodium chloride. It remained sterile on culture.

Further chest films showed a left pleural effusion. At cardiac catheterization normal pressures in the right side of the heart were found. Angiocardiography showed no abnormality of the pulmonary arterial tree.

The discharge from the sinus continued until 10 weeks after admission when a left thoracotomy was performed. An irregular tumour was found lying anterior to the aortic arch in the anterior superior mediastinum with ramifications extending anterior to the pericardium, to the right side of the thorax, and anterior to the right common carotid artery into the right side of the neck. The tumour was dissected out leaving the upper limits of the cervical extension which could not be reached with safety.

Microscopically, the tumour was found to be a teratoma of a high degree of differentiation. It contained muscle, intestinal and pancreatic tissue, connective tissue, blood vessels, nerves, keratinized squamous epithelium with hair and sebaceous glands, and ciliated respiratory epithelium. There was no evidence of malignancy.

The patient was followed up for seven years and remained well with no change in the radiograph. Her eldest child, born before the illness described, died of a cerebral tumour. She had two more children. She was lost to follow-up when she emigrated.

CASE 2

A 27-year-old Chinese Malaysian woman was referred from Kuala Lumpar where a diagnosis of mediastinal teratoma had been made. She had complained of intermittent chest pains for seven months, and two weeks before admission had developed a dry cough. A chest radiograph had shown a mediastinal mass and she received radiotherapy to a total dose of 1000 rads. Exploration through the neck confirmed a mass in the thoracic inlet. Mediastinoscopy and bronchoscopy were not possible.

On admission to the Brompton Hospital in April 1972 there was dullness to percussion over the upper anterior chest wall. There was also tender pitting swelling of the upper anterior chest wall extending into the suprasternal notch. A chest film showed a 7 cm rounded mass in the anterior part of the left side of the superior mediastinum in front of the arch of the aorta (Fig. 1). It blended inferiorly with the main pulmonary artery and extended upwards to the left sternoclavicular joint. The trachea was displaced backwards. A little calcification was seen in the mass. Full blood tests showed mild hypochromic anaemia (haemoglobin 10·3 g/dl) and the ESR was 81 mm/hour (Westergren).

As a provisional diagnosis of reticulosis seemed most likely, a mediastinal exploration was carried out through a left parasternal incision with division of the third and fourth costal cartilages. A cystic tumour filled with hair, sebaceous material, and turbid fluid was found, a biopsy obtained, and the cyst closed with a suction drain left outside it. Microscopy of the biopsy showed part of a simple benign dermoid cyst. Culture of the fluid was sterile.

Following this diagnostic procedure the wound failed to heal satisfactorily and eventually broke down, discharging cyst fluid and sebaceous material. Over the next four weeks there were recurrent episodes of pyrexia with extensive inflammation around the wound and a persistent discharge of clear fluid. This was repeatedly cultured but remained sterile. Blood cultures

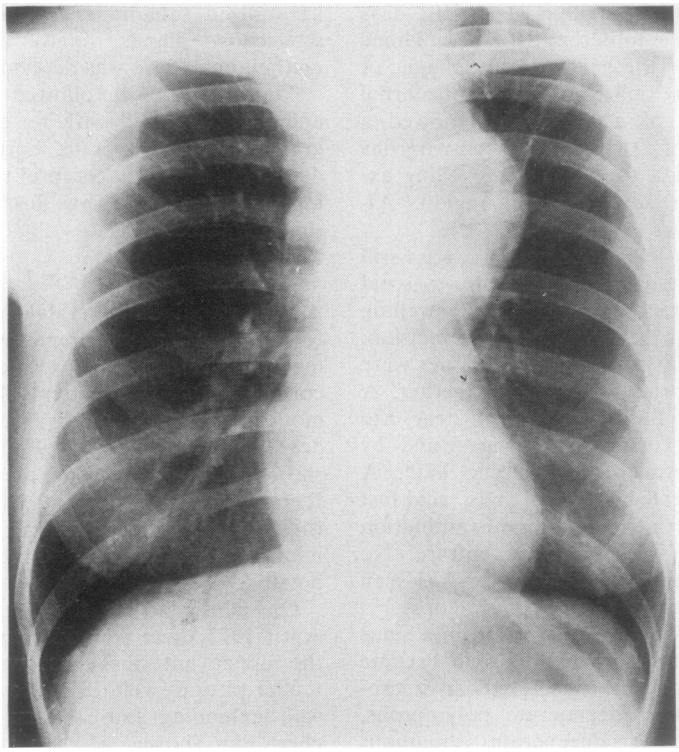

FIG. 1. *Case* 2. *Chest radiograph showing the mediastinal tumour.*

during a febrile period were also negative. Unfortunately, the fluid was not examined biochemically.

Finally, one month after mediastinal exploration, it was decided to proceed with operative removal although the wound was still not completely healed and intermittently discharged fluid. Through a sinuous incision incorporating the previous anterior wound, the sternum was split. The tumour was found to be densely adherent to the back of the manubrium and the body of the sternum. Above, it extended 2 cm above the suprasternal notch and below, it was firmly attached to the pericardium. It surrounded the left innominate vein. Laterally, a very thick fleshy right lobe of thymus was attached to the main mass; no left lobe of thymus was demonstrated. Posteriorly, the tumour was closely adherent to the trachea. The tumour mass was dissected out with adherent pericardium. The cut specimen is shown in Figure 2.

Microscopy of the specimen showed it to contain connective tissue, skin structures (including hair), probably respiratory and alimentary epithelium, and exocrine structures of the pancreas. There was no malignant change. Apart from a little residual inflammation at the upper end of the incision, which healed rapidly, postoperative recovery was satisfactory. At the time of writing, two years after the operation, the patient remains well.

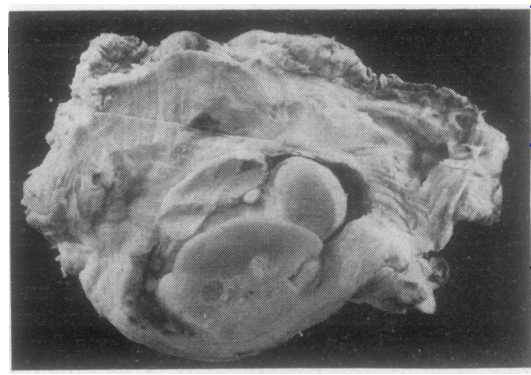

FIG. 2. *Case* 2. *Cut surface of the specimen removed at operation showing the mainly solid, variegated tumour with the central cavity lined by hair-bearing skin* (×0·8).

DISCUSSION

There seems little doubt that the inflammation occurring around these teratomata was not bacterial in origin. In case 1, amylase was found in the discharge which followed exploration of an inflammatory mass when the tumour was probably not disrupted. It seems reasonable to suppose that leakage of digestive enzymes from the tumour was the cause of the inflammation. The inflammation followed, but seems unlikely to have been related to, a 400 rad dose of radiotherapy. In case 2, inflammation followed 1000 rads of radiotherapy and mediastinoscopy and biopsy in the patient's native country. Enzymes were not looked for in the discharge. However, the discharge was sterile and as the tumour in this case, as in case 1, contained pancreatic and intestinal mucosa, it is likely that the cause of the inflammation was similar. The clinical course certainly bore close resemblance to that of case 1. In each case the cellulitis was of a particularly florid type and the discharge persistent.

Non-infective inflammation around mediastinal teratomata has been mentioned occasionally in the literature. Hertzler (1916) described a patient whose benign dermoid cyst produced bulging of the chest wall and redness of the overlying skin. He suggested that the inflammation may have been chemical 'as occurs in wens'. Marsten, Cooper, and Ankeney (1966) described a case of perforation of the pericardium by a benign teratoma which contained intestinal mucosa and pancreatic tissue. They found inflammation around the tumour and stated that there was no evidence of infection but gave no bacteriological details. Microscopy suggested that the inflammation may have been due to the irritant effects of sebaceous material and hair. This is an alternative hypothesis for the inflammation, particularly in case 2, reported above. However, as most authorities believe that all teratomata, including the apparently simplest dermoid cyst, can be found on meticulous examination to contain tissues of each germ layer, any teratoma is likely to contain intestinal, pancreatic or salivary tissue, and this may be the cause of such cases of non-infective inflammation. Similarly, Rosenbluth, Steinberg, and Dotter (1952) described a patient in whom a mediastinal dermoid had resulted in myocardial abscesses. The pus looked unusual, no organisms were seen on direct smear, and organisms which grew on culture were suspected of being contaminants.

Infection is frequently cited in the literature as a complication of teratomata (Heuer and Andrus, 1940; Rusby, 1944; Burnett, Rosemond, and Bucher, 1952; le Roux, 1960; Whittaker and Lynn, 1973) but bacteriological details are rarely given. It may be that some of these cases are not infective but are similar to the cases described.

In other cases the initial increase in size of the teratoma seems to have been non-infective. This results in rupture, for example, into the pleural cavity, when the fluid may be initially sterile (Hedblom, 1933; Wheeler, 1939; Hanten, Keyes, and Meyer, 1955; Thompson and Moore, 1969) but infection may follow intervention such as drainage (Wheeler, 1939).

True bacterial infection does occur. There has been much discussion about the source and route of infection. Infection from the bronchial tree (with or without a fistula) and from the blood stream have been suggested (Heuer and Andrus, 1940; Rusby, 1944; Whittaker and Lynn, 1973). While infection through a fistula seems a likely explanation, the cause when there is no fistula is more doubtful. Infection is rarely described in other mediastinal tumours where blood-borne infection could also occur. It may be that inflammation and necrosis caused by release of digestive enzymes provides a nidus for secondary bacterial infection in some cases.

Similarly, a satisfactory explanation has not been given for the high incidence of fistulae into the bronchial tree associated with teratoma (Graham, Singer, and Ballon, 1935—1 case; Ringertz and Lidholm, 1956—1 case; Inada and Nakano, 1958—4 cases; Daniel *et al.*, 1960—1 case; le Roux, 1960—2 cases; Lindskog, Liebow, and Glenn, 1962—1 case; Boyd and Midell, 1968—4 cases; Benjamin *et al.*, 1972—I case) and also to the pericardium (Cordes, 1859; Akman, 1948; Aktan, 1961; Marsten *et al.*, 1966), to the aorta (Cordes, 1859; Kolpak, 1951), to the superior vena cava (Stein, 1917), to the oesophagus (Herlitzka and Gale, 1958), to the pleural cavity (Gordon, 1930; Harrington, 1933; Hedblom, 1933; Wheeler, 1939; Hanten *et al.*, 1955; Thompson and Moore, 1969) and externally through the neck (Gordon, 1930). In all of these cases where details were given the teratoma was benign. Although several were said to be simple dermoids, they might also be expected to contain endodermal structures. Fistulae are rarely described with other mediastinal tumours. Direct invasion seems unlikely in benign tumours. Infection is given as a possible cause but the same reservations apply. Pressure necrosis may be the mechanism (Hertzler, 1916), but it is surprising that this seldom occurs with other mediastinal tumours. It

may be that inflammation and necrosis caused by digestive enzymes leaking from the tumour, after causing its expansion and rupture, may also be a mechanism for fistula formation.

An explanation for the rarity of infection and fistulization of malignant teratomata may be that they do not usually contain well-differentiated functional tissues (Schlumberger, 1946) and would therefore be less likely to secrete digestive enzymes.

The concept of the varied tissues of teratomata performing their normal functions is not new. Ectodermal structures often develop normally; hairs and teeth grow and sebaceous glands produce sebaceous material. Ovarian teratomata may produce thyroid hormone (Brown, Shetty, and Rosenfeld, 1973). Chorionic gonadotrophin may be produced and may lead to a positive Ascheim-Zondek test. Gynaecomastia caused by a malignant mediastinal teratoma producing chorionic gonadotrophin has been described (Rubush *et al.*, 1973). Hypersecretion of insulin has been reported in a benign mediastinal teratoma which contained pancreatic tissue (Honicky and de Papp, 1973). It is not surprising, therefore, that the exocrine function of pancreatic tissue also occurs, as appears to have happened, with unfortunate consequences, in the cases described. The secretory function of intestinal and salivary epithelium could also occur with similar results. Both normally secrete amylase but any digestive enzyme, such as trypsin, chymotrypsin, and pepsin, could have the same effect. Alimentary mucosa occurs commonly in teratomata; pancreatic tissue occurs less frequently and is always associated with intestinal cavities and, sometimes, with gastric tissue (Willis, 1962). Pancreatic tissue is said to occur more frequently in mediastinal than other teratomata (Schlumberger, 1946).

If the condition is recognized it would seem from the experience of these two cases, and on theoretical grounds, that it could be expected to take a protracted course, and early removal of the tumour would be the best management. It is possible that enzyme inhibitors like Trasylol could be helpful for short-term use.

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