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Squamous Epithelial Cancer in Metaplastic Pleura Following Extrapleural Pneumothorax for Pulmonary Tuberculosis*

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Summary. During the period 1947–1955, 148 patients underwent extrapleural pneumolysis for pulmonary tuberculosis in Stockholm City Chest Hospital at Söderby. In 121 tuberculosis healed following operation. Ten of these later developed pain and a feeling of tension on the operated side and were operated upon with evacuation of the extrapleural sac. In four of them a highly differentiated keratinizing squamous cell carcinoma had developed. In addition, two more cases of carcinomas of the same type operated on at other hospitals are described. Five of the six patients died of cancer. Squamous cell carcinoma occurring in metaplastic mesothelial cells has hitherto not been reported on and the phenomenon is discussed and compared with the more common scar cancers within lung tissue caused by damage from tuberculosis.

Key words: Mesothelium — Tbc — Metaplasia — Squamous cell carcinoma — Extra pleural pneumothorax.

Introduction

Scar cancers in the lung following pulmonary tuberculosis have been described previously. The sequence of events includes fibrosis, lymphatic stagnation causing trapping of anthracotic pigment, metaplasia of alveolar and bronchiolar epithelium followed later by development of a cancer (Rössle, 1943). The six cases of pleural cancer which are presented below all have features in common and are regarded as a group with a common etiology. In all the cases an extrapneumolysis had been performed for pulmonary tuberculosis and the subsequent collapse of the lung was maintained for several years with refills of air in the extrapleural space. When the refills ceased a sterile effusion collected in the space, followed after a variable period by symptoms suggestive of increasing local fluid pressure. Investigation then showed fibrosis, metaplasia and the development of a cancer in the tissues of the extrapleural space.

Patient Material and Clinical Results

Between 1947–1955, 148 patients—80 men and 68 women—underwent extrapleural pneumolysis for pulmonary tuberculosis at the Stockholm City Chest Hospital. In 121 cases no relapse occurred (82%) but those that did relapse were treated chemotherapeutically or

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by lobectomy or thoracoplasty. The subsequent follow-up period was 14.4 years. Fifteen patients died, 104 were followed for 10 years, 22 patients for between 5 and 10 years, and 7 for less than 5 years. Extrapleural pneumothorax was maintained for up to 134 months with a mean duration of 43 months and the number of refills varied between 2 and 150 with a mean number of 86.

Four patients developed a squamous cell carcinoma and four showed metaplasia but no cancer in the extrapleural sac at reoperation. The clinical data of the 4 patients who developed squamous cell carcinoma in metaplastic mesothelium have already been described by Bruce et al. (1960) together with an additional case from Västerås. The sixth case (case B2) was seen at the University Hospital, Uppsala in 1974. This latter patient had had a left-sided extrapleural pneumothorax carried out in March 1953 which was maintained by air refills until April 1957 when they were discontinued as the pulmonary lesions appeared to have healed. The extrapleural space subsequently filled with fluid. In January 1968 massive pleural thickening was noted on X-ray but it was not until April 1972 that the patient experienced some difficulty in swallowing. In October 1972 left-sided chest and shoulder pain caused a needle biopsy to be done but only squamous epithelial cells were found. Two months later some keratin and parakeratotic squamous epithelial cells were seen at a further needle biopsy. In January 1973 the extrapleural sac was removed and decortication of the lung carried out. The sac contained soft cheesy material and there was a tumour mass which had eroded two overlying ribs but on microscopy no neoplasm was found. In September 1973 a further operation showed a tumor mass invading the uppor thorax growing into the mediastinum. The tumor was removed together with fragments of destroyed ribs. Microscopy then revealed a well-differentiated squamous cell carcinoma. The later onset of chest pain, finger paraesthesia, and fever necessitated a course of irradiation and bleomycin injections but the patient died 8 months following the removal of the tumour.

A summary of the 6 cases is given in Table 1. The ages of the patients were 28, 41, 42, 48, 53, and 63 and the cancers appeared 47, 48, 48, 48, 60, and 81 months, respectively, after the initial extrapleural pneumothorax had been established. Over a 100 air refills had been done on each case and the onset of symptoms due to the development of a cancer varied between 8 months and 15 years. Of the 6 cancer patients, 4 had died within 3 years of its discovery, 1 died postoperatively, and the sixth is alive.

Pathology

Case 1 (No. 88). The resected pleural sac was 10 mm thick and on opening it there was a fungating mass of growth with a broad base, 5 cm across. The sac wall was not infiltrated by tumor and the growth lay beneath the ribs. Microscopy showed most of the sac lined with normal mesothelial cells but at the base of the well-differentiated squamous cell carcinoma there was squamous metaplasia of the mesothelium.

Case 2 (No. 96). On opening the resected pleural sac a large tumor mass bulged inward on the rib side. Microscopic examination showed a highly differentiated keratinizing squamous cell carcinoma arising from the mesothelial surface of the sac. The remaining mesothelial surface showed some squamous metaplasia. Carcinoma had spread locally outside the pleural sac itself and the subsequent clinical course was suggestive of extension of growth into the base of the neck. The patient died 3 years later.

Case 3 (No. 99). A pleural sac with extensive fibrosis together with the upper lobe of the lung were removed. The sac consisted mainly of firm growth which had invaded the mediastinum along the vascular sheaths. Radical extirpation was not possible. Microscopy revealed a moderately well-differentiated, partly keratinized, squamous cell carcinoma derived from metaplastic pleural tissue. The upper lobe of the lung showed only healed tuberculosis. At the subsequent autopsy local spread had occurred within the thorax around the blood vessels and metastases were present in the local lymph glands and in the vertebrae.

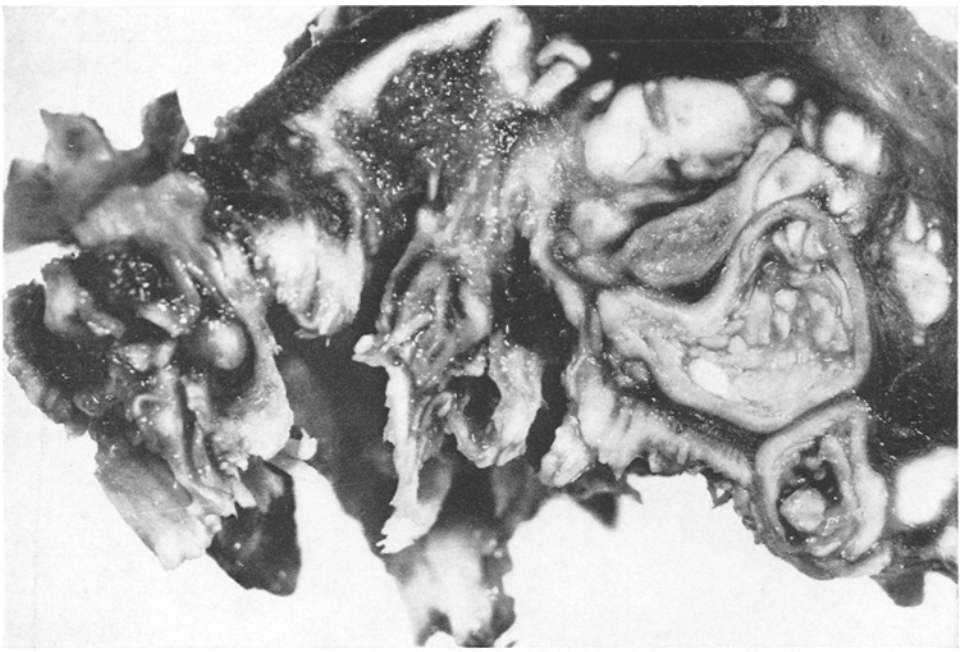
Case 4 (No. 103). The resected pleural sac and upper lobe of the lung showed no macroscopic evidence of growth but microscopic examination showed a well-differentiated squamous cell, keratinizing carcinoma with some squamous metaplasia of the residual mesothelial lining. Later, autopsy showed that local spread of tumor had occurred into the diaphragm, liver, and ribs.

Table 1. Patients with cancer or metaplasia following extrapleural pneumolysis

Pat. No.	Sex, Age	Age at cancer metaplasia debut	Maintenance ex.pl. cav. months	Number of refills	Interval between cessation of refills and onset of metaplasia or carcinoma	Diagnosis	Treatment	Follow up
6	♀, 18	45	47	110	9 years	metaplasia	operation only	19 years, alive and well
88	♀, 14	42	48	100	8 months	cancer	operation only	20 years, alive and well
96	♂, 10	48	47	90	1.9 years	cancer	operation only	died from cancer 3 years
99	♂, 17	41	60	110	3.4 years	cancer	operation + palliative radiotherapy (2,500 rads)	died from cancer 1.5 years
100	♀, 25	35	45	90	3.6 years	metaplasia	operation only	17 years, alive and well
101	♀, 07	53	61	120	4.8 years	metaplasia	operation only	17.5 years, alive and well
103	♂, 30	28	81	140	2 years	cancer	operation + radiative therapy (5,300 rads)	died from cancer 3 years
107	♀, 30	29	51	110	4.9 years	metaplasia	operation only	18 years, alive and well
B1	♂, 93	63	48	?	5 years	cancer	operation only	died from post op. bleeding
B2	♂, 20	53	48	98	10 years (15) years	cancer	operation radiotherapy 3,000 rads bleomycin	died from cancer 1.5 years

Case 5 (No. B1). The pleural sac and upper lobe of the lung were resected. Two ribs and three vertebral bodies were invaded by "granulation tissue." Microscopic examination showed a well-differentiated, keratinizing, squamous cell carcinoma growing in thickened connective tissue but there was no growth in the lung tissue. The patient died postoperatively from uncontrolled bleeding from tumor infiltrated vertebrae.

Case 6 (No. B2). A pleural sac together with four overlying ribs were excised. The inner surface of the sac showed a rough surface covered with papillomatous masses. Growth was observed deep within muscle tissue outside the sac (Figs. 1, 2). Keratinizing plaques were also observed lining the sac surface. Microscopic examination of the sac showed it was lined by mesothelial cells which in places proliferated to form small knobs in which keratin could be found. In other parts a well-differentiated, squamous cell carcinoma was present. The well-differentiated nature of the carcinoma made its recognition on cytologic grounds alone very difficult. The penetration of surrounding muscle tissue combined with infiltration of skeletal tissues showed that it was carcinomatous and not merely a metaplastic change.



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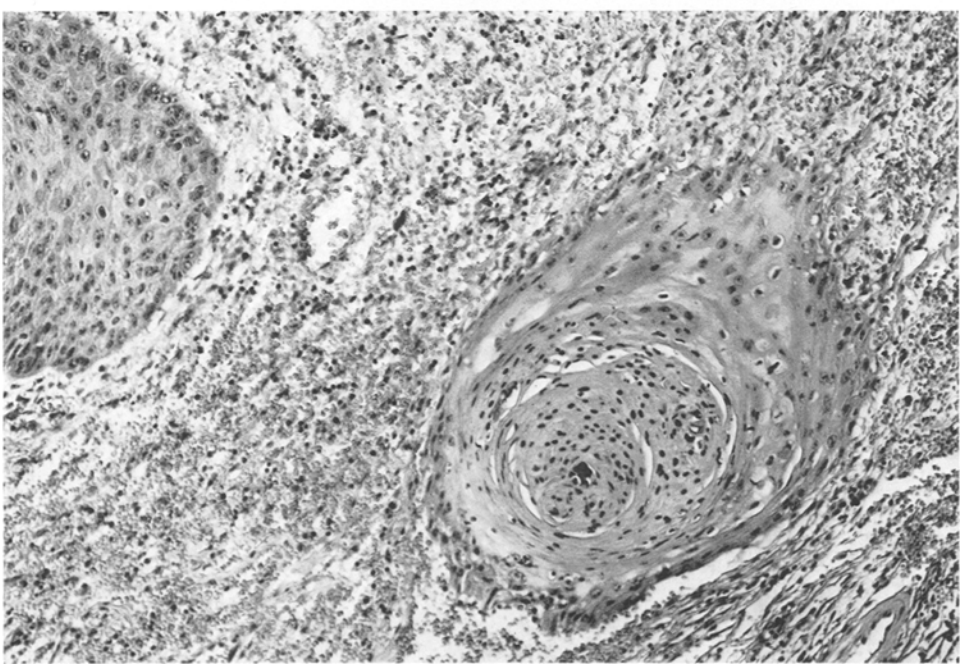

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Fig. 1. Macroscopic specimen from patient B2 showing intercostal muscles and a polypous, highly keratinized squamous cell carcinoma within pleural and scar tissue. Note small infiltrating white nodular tumors within muscular tissue. × 10

Fig. 2. Well-differentiated, keratinized squamous cell carcinoma with infiltrative pattern. Hematoxylin-eosin × 40. Patient B2

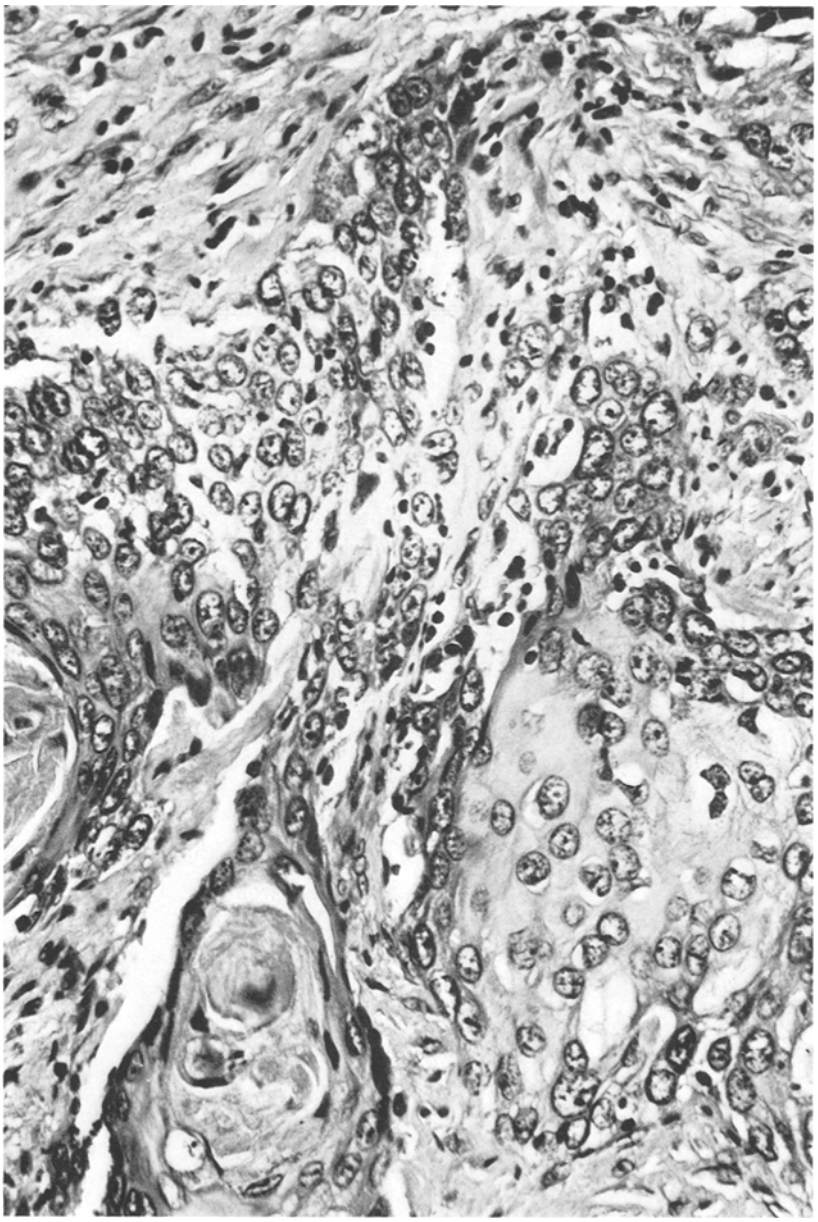

Fig. 3. Patient 99. Mesothelial cells with hyperplasia and atypia as well as intracellular keratinization with progression into squamous cell carcinoma. Hematoxylin-eosin × 250

Discussion

Extrapleural pneumothorax had been performed in all these patients 4–5 years previously. When air refills stopped sterile effusions accumulated in the extrapleural space resulting in a failure of the space to obliterate, and its lining

mesothelium underwent metaplastic change. The time interval between cessation of air refills and the first appearance of symptoms referable to changes in the extrapleural sacs ranged from 8 months to 10 years. The diagnosis of cancer was established in case 2 by cytologic examination of pleural fluid and in case 1 by the discovery of a suspected tumor shadow after drainage of the extrapleural space. In all the cases the excised tissue showed a very thickened pleura, proliferating elastic tissue, pigmented areas, and metaplasia of the lining mesothelium. The metaplastic tissue contained keratinized areas which subsequently developed into well-differentiated squamous cell carcinoma. The type of neoplasm was similar in all cases and appeared to have arisen from the pleura. Five of the patients died from spread of the carcinoma but case 1, in which pleural infiltration and penetration had not occurred, is still alive 15 years after its removal. In all cases the tuberculous infection in the underlying lung appeared to have healed. Because pulmonary tuberculosis often occurs in young persons several of the patients were still young when they developed their carcinoma.

The development of carcinoma in the pleura following extrapleural pneumothorax is an entity which first becomes apparent after the air refills were discontinued and was preceded by fluid effusion into the unobliterated space. The treatment of choice for these very well-differentiated, squamous cell cancers appears to be surgical extirpation.

Local factors can be discounted as a cause for these cancers as our cases were drawn from three centers. Although earlier investigators (Robertson 1924; Willis, 1952) were skeptical of the existence of primary pleural tumors, McCaughey (1958), Campbell (1950), and Goodwin (1957) have all shown that such tumors exist, and that they arise from the mesothelial cells, and that they possess the pluripotentiality of mesothelium. Liebow (1952) considered that squamous cell cancer was the most dubious form of pleural tumor, but mesothelium may assume squamous features in conditions of chronic irritation. The squamous cell metaplasia may be difficult to differentiate from a well-differentiated squamous cell cancer as is shown in this series of 6 cases.

Among the 126 cases of pleural tumors reported to the Swedish Cancer Registry between 1959–1965, 3 were squamous cell cancers and each of these had resulted from extrapleural pneumothorax.

Scar cancers in the lung as already stated have been recognized for many years (Rössle, 1943; Meyer et al., 1965). Such cancers arise in relation to dense and often pigmented scars due to tuberculosis and infarcts in the lung. The scar cancers are mainly found in the upper lobes and a considerable proportion of them are adenocarcinomas (Carrol, 1962; Yokoo et al., 1961; Spencer, 1968). A relationship to tuberculosis has long been suspected (Themel et al., 1955). The tendency of epithelium in the lung to undergo metaplasia was shown by Barnard and Day (1937) and this seems to occur when epithelial cells become trapped in fibrous tissue or in those alveoli abutting upon lung scars (Berkheiser, 1959, 1963; King, 1954). The same changes occur in the presence of chronic interstitial lung fibrosis (Meyer et al., 1965; Berglund et al., 1972). Squamous cell metaplastic changes can also occur in the peripheral parts of the lung (Meyer et al., 1965; Heppleston, 1956).

Anthracotic pigmentation is commonly seen in such lung scars due to lymphatic blockage (Raeburn et al., 1957) together with elastoid proliferation (Heppleston, 1956). Although adenocarcinomas are most commonly encountered in these scars

areas of squamous cell cancer also occur (Yokoo et al., 1961; Carrol, 1962) and are more commonly seen within subpleural scars. Balo et al. (1956) described the sequence of epithelial proliferation in the scars which cause first metaplasia followed by the occasional development of squamous carcinoma and adenocarcinoma.

Although BCG vaccination has been used in an endeavour to destroy malignant cells by activating the T-cell series of lymphocytes, the presence of previous tuberculous disease in these patients and therefore the presumed stimulation of their cellular immune mechanisms failed to arrest the progress of their tumors.

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