Archiv für Gewerbepathologie und Gewerbehygiene, Vol.13 : 382-392, 1954.

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PRIMARY EPITHELIAL TUMOR OF THE PERITONEUM IN ASBESTOSIS.

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With 10 figures in text.
/Received for publication August 17, 1954/.

In contrast with the dust of silica, it may be considered proven that dust of asbestos can trigger autonomous tumorous growth. Particularly pulmonary cancers have been often described in connection with asbestosis /Egbert and Geiger, Nordmann, Linzbach and Wedler, Holleb and Angrist, Welz, Boemke, Curetn, Hueper, König and others/ Hueper could compile 55 such cases up to 1950. In contrast with an average of 1-1.4 % of bronchial and pulmonary cancers among general population, the number of pulmonary cancers in asbestos workers in Germany, according to Boemke, amounts to 12 - 25 % /Nordmann 17 - 20 %, Welz 20 %/, according to Hueper in the world literature to 13 - 15 %, in England including cancers of the pleura to 13 %. Nordmann and Sorge could prove experimentally that in long-term dusting of the lungs with asbestos the cancer develops through metaplasia of the bronchial epithelium into flat epithelium. Thus in to-date ascertained pulmonary cancers of the asbestos workers in 5/6 it was flat epithelium carcinoma, which in the majority of cases is located in the lower lobes /Homburger, Kahlan et al./. In the mean-time also 3 carcinomas of the pleura have become known in the German literature /Teutschländer, Alwens, Fischer-Wasels /1/, Weiss/, in England equal observations have been made.

Primary tumors of peritoneum, however, have not yet occurred in asbestosis, as far as the available literature is concerned. Let us, therefore, report on a primary tumor of the epithelium of the serosa in pulmonary asbestosis, and let us discuss the question of causal relationship of both diseases.

W.K. [1], 53 years old, was 1919 - 1951 active in an asbestos factory, 26 years of it as yarn- and asbestos spinner.

1/ Cordial thanks to Dr. K.Tiefensee, Schwäbisch-Hall, and Prof. Dr.H.Dennig, Stuttgart, Karl-Olga Hospital, for letting us have the patient's record.

A heavier exposure to dust was there in 1919 - 1930 and in 1940-1945, i.e. together for 16 years. In 1937 asbestosis O-I was ascertained in the Charité, Berlin. In the beginning of 1952 medical notification of an occupational disease under title Asbestosis of the lung was made on basis of the history, of the radiological finding and of the finding of asbestosis bodies in the sputum.

In 1947 K. was treated 9 weeks in hospital for exudativ pleuritis. In the spring 1950 during a rutine examination of all employees scattered calcified foci in both lungs were found and pleural plaques with bony deposits and formation of adhesions on the left side, but no active tuberculosis. Since May 1951 increasing back pains have developed with increase of sedimentation rate of red blood cells from 2 to 47/80 mm. Radiologically in spite of multiple examinations of the lumbar spine only spondylotic changes were found without signs of caries. In November 1951, at hospitalisation done because of radiating pains in the lumbar spinal area, of fever, of loss of apetite and of loss of weight, cancer of the prostatic gland could be ruled out. In the lungs there were many old specific disseminated foci and on the right side an indurative infiltration with calcification on X-rays. Intercurrently developed pericarditis with damage to myocardium and with serious circulatory impairment. Since acid-fast bacilli were found in the sputum it was assumed that there was an open active, predominantly productive tuberculosis of the lungs with tuberculous pleuropericarditis. At transfer to speciality-medical care the tubercle bacilli were never found but found were asbestos bodies. In addition, the chest radiogram showed a fine honeycomb pattern in both lower lobes with a sharply delimited hard infiltration of a wallnut size in the right lower field, by which finding diagnosis of pulmonary asbestosis appeared surely established. Beside lumbar and lower spine pains intercurrent kidney colics occurred without finding of concrements or signs of a tuberculous condition. In mid April 1952 the patient was transferred back with diagnosis of asbestosis of the lungs with pleuro-pericardial inflammatory signs. In the end of July 1952, during so far stationary pulmonary condition developed a fresh infiltration of the size of a 5 Mark coin in the right lower field with blood in the sputum. In mid August 1952 appeared a tuberculous

leptomeningitis, with confirmation of bacilli in spinal fluid by animal experiment, which led under increasing loss of consciousness and cachexia to death on September 15, 1952.

Autopsy /No 751/ revealed following diagnosis : Leptomeningitis basilaris tuberculosa with a moderate hydrocephalus internus and generalized brain edema. Spondylitis tuberculosa of the 3rd and 4th lumbar vertebra with large bilateral abscesses along the psoas muscles. Old partially calcified tuberculosis of both seminal vesicles, epididymis and prostate. Extensive scarring tuberculosis of pulmonary upper lobes with small cavities bilaterally. Mixed-infectious tuberculous subpleural bronchiectasis in the right lower lobe. Bilateral tuberculous pleuritis with residual empyema on the right side and with complete bilateral obliteration with pleural plaques and calcifications. Pericarditis healed by obliteration. Hematogenous dissemination of tuberculous foci in the lungs, in the spleen and in the right kidney. Universal cachexia of a high degree. Asbestosis II of the lungs with moderate diffuse fibrosis of pulmonary parenchyma /fig.1, . Scanty asbestosis of the regional lymphnodes, asbestosis bodies in the spleen /fig. 3/. Chronic catarrho-purulent bronchitis and peribronchitis with focal miliary purulent branchopneumonias in both lungs. Light hypertrophy of the right heart. Moderate congestion of organs.

Nephrolithiasis of both sides with kidney- and bladder-grit, dilatation of the renal pelvis, chronic catarrhal cystitis and pyelonephritis. Stercoral ulcers in the rectal mucosa. Atherosclerosis I of the coronary arteries and of the ascendens aorta.

Local finding in the abdominal cavity : On the mesenterium and on the abdominal viscera, particularly in the ileocecal region, there were partly stripe- and netform gray-white thickenings of the serosa with many nodules of pinhead up to millet seed size. Particularly extensive confluent conglomerates and solid gray-white plaques were located predominantly on the bottom face of the right diaphragm /fig.4/ as well as on lateral serosa, and scattered also on both liver lobes and in the left subphrenic region. One plaque of a hand-palm size over 1 cm thick composed of whitish solid tissue with glassy-colloid cutting surface was found in the Douglas' recess /fig. 5/. Histologically peritoneum everywhere showed rich proliferation and strong swelling of epithelium which partly created cubic

agglomerations and multilayer cell depositions. Proliferation of the epithelial cells was strongest in the area of many fibroepithelial villous-papillary formations /fig. 6,7/ whose stroma was mostly solid fibrotic with few cells. Next to it there were irregular thickenings, nodular and flat formations, made up of a fine network fib with deposition of mucoid substance in the mesh. Beside the branching myxomlike mesenchymal cells there were scattered big cells with irregular margins with strong polymorphy of the cells and nuclei, withfine staining protoplasm and with vacuoles of size as big as leading to formation of a signet ring /fig. 8/. Occasionally there also were polynuclear cells as product of a direct nuclear division but no miteses. Subserosa in this area was thickened by layers of fibrotic connective tissue with scattered infiltrations of round cells. There were all transitions from villous-papillary fibroepithelial proliferations over polyplike loose tissue proliferations to diffuse plaquelike thickening of the peritoneum.

The tissue plaque in the small pelvis was predominantly composed of polymorphous macrocellular proliferations, between which penetrated a fine mesh partlynot yet stainable for collagen, with secretion of mucoid intercellular tissue. Often there also were small fissures and small cystic cavities with very rich macrocellular epithelial lining in desquamation /fig. 9,10/ which resembled proliferation of mucosa of the villi. In between amply lay fine septa containing vessels with strong inflammatory cellular infiltration and with phagocytes richly pigmented by hemosiderin analogous to depositions of iron pigment in an asbestotic pulmonary tissue. Typical asbestos needles or asbestos bodies could not be found in spite of thorough search of many histological preparations. On the other hand small amounts of asbestos could be detected in the tumor tissue roentgenographically /1/.

Thus there was a primary, partly villous-papillary, partly mucoid-transformed epithelial tumor of the peritoneum with partly nodular plaquelike growth.

Pleural thickenings still contained rests of the

1/ The rentgenographic fine-structural analysis was made by docent Dr.Pfefferkorn in the Institute of Hygiene of Münster University /Prof.Jötten/.

tuberculous granulomatous tissue but no tumorous changes. Existence of a primary epithelial tumor of the pleura was ruled out by this.

Discussion :

Primary tumors of the peritoneum belong to the biggest rarities, particularly in their diffusely spreading form. Therefore it had to be thought from the beginning of a combination of pulmonary asbestosis with a primary epithelial tumor of the peritoneum, particularly with regard to close relation of deposition of asbestos dust to tumors of the lungs and pleura. Thus it must be first determined whether there is an accidental event here, or whether a causal relationship between deposition of asbestos and the peritoneal tumor can be proven, or at least can be made probable.

While it was hesitated in the past whether peritoneal tumors originated from lymph-vessels or from epithelium of the mucosa, today they are almost generally derived from the celomic epithelium and preferably called, with Marchand, malignant epithelial tumors rather than synonymously endotheliomas, mesotheliomas or malignant peritoneal epitheliomas. Due to pluripotent abilities of the celomic epithelium histological structure of these tumors is subject to very big variety, both in an individual case and in the various observations - quite analogous with primary epithelial tumors of the pleura and pericardium - which is to be expected in embryologically identical serous surfaces of an essentially identical structure /Prinz/. Quite in agreement with the various potentials of differentiation in tissue cultures of the pleural mesothelioma /Sano, Weiss and Gault/ also in man occur sarcomatous forms of growth /Greer/, partly with mucous-myxomatous transformation /Rhnid and Wright/, beside formation of fissures and cavities and villous-papillary and polypous growth /Fischer, Klein and Rarei/ whose individual components appear partly predominantly and partly in motley mixture. Greer in 1950 estimated the number of the true diffuse peritoneal sarcomas in the literature to 15. Also the other forms of epithelial tumors in the abdominal cavity must be substantially rarer than primary tumors of the pleura, the number of which in autopsy material, approximately 1 ‰ , is already very small.

Villous-papillary and small-nodular parts of our peritoneal tumor showed in part big similarity with nodules and

villi of the serosa which are not a rare finding on serous surfaces, and which, according to older animal experiments of Tsunoda, are due to chronic mechanical irritation, equally as tendon formations of the pericardium and plaques of the serosa. According to Tsunoda, Herxheimer and Mönckeberg, the changes begin with injury to epithelium to which reactive proliferation of connectiv tissue follows. Other authors considered these formations to be mainly inflammatory, partly mechanically provoked. Prinz does not see in them expression of an inflammation but rather thinks that their causal origin is an extraordinary permeability of the vessels, or an injury to vessels, because so often there is edema at the onset.

Quite similar morphologic findings could Behrens produce in mice by intraperitoneal application of suspension of chrysotile-asbestos in water : In the early phase of 2-3 weeks, around the asbestos fibres appear nodular inflammatory infiltrations of pin-head size with immigration of histiocytes. A connective tissue incapsulation followed with continuing phagocytosis in the nodules. Later intracellular depositions of iron-dust was observed on the periphery and after 10-12 months image of a fibrous late phase was reached. Vorwald, Durkan and Pratt in identical experiments only observed reaction of connective tissue in case of intraperitoneal injection of long asbestos fibres and concluded that asbestosi is not caused chemically but by unusual mechanical irritation of the tissue which comes from flexibility of the asbestos fibres. These experiments agree with results of King obtained by intratracheal instillation of suspensions of asbestos dust in which also only fibres above 15 micron of length could produce a nodular reticulosis while shorter fibres only led to interstitial reticulosis without formation of nodules.

Toxic effect of chrysotile asbestos or phenomena due to dissolving of asbestos fibres could never be found by Behrens. Therefore he evaluated, like also earlier Gardner and Cummings et al. the nodular fibrosis as an unspecific reaction to foreign body. Also investigations of Belt, Friedmann and King on cell cultures which only showed slow phagocytosis of asbestos dust without influenc on growth of the fibroblasts, do not necessarily point to toxic cell damage, in contrast with opinion of Beger. In favor of a

mechanical action of asbestos dust had already earlier expressed themselves DiBiasi as well as Sundius and Bygdén, among others.

As for asbestotic fibrosis, also for carcinogenesis in asbestos workers, according to current experiences, mechanical injury to the tissue should be quite in the foreground while chemical toxic effect clearly stands in the background, and e.g. by Linzbach and Wedler is completely rejected. Cancerogenic effect thus appears to be consequence of overshooting regenerative procedures of irritated tissue in the sense of Fischer-Wasels /2/ which is triggered by permanent mechanical foreign-body irritation by the asbestos fibres and maintained by their flexibility and great inability of resorption. The starting foreign-body reaction apparently never comes to complete standstill, particularly when asbestos dust penetrates, at inhalation or later, into areas which are constantly in motion, such as e.g. lungs, pleura or also the abdominal cavity. Absence of any foreign-body reaction worth mentioning around asbestosis bodies in the spleen and the lymphnodes of our case could indeed have its deeper cause in absence of motion stimulus at these points of deposition. Long latent periods from beginning of exposure to dust to formation of tumor in the lungs and pleura of 16-25 years in average is understandable by constant and mild mechanical irritating effect of asbestos dust on the reactive fibrosis and on the adjacent tissues.

We could see, as a quite general principle, in the permanent mechanical irritation of the tissue by asbestos fibres deeper basis for carcinogenesis in the sense of the Ribbert's theory of irritation. This modus of origin downright imposes itself in our case in comparing the peritoneal tumor with the nodules and villi of the serosa of inflammatory-mechanical origin, and particularly with intraperitoneal experiments with asbestos dust. The villous-papillary and nodular proliferations gave clear impression of a reactive and by long term chronic mechanical and inflammatory irritation maintained, processus of regeneration which during the time had provoked an overshooting proliferation of epithelium with increasing atypia and progressing anarchic growth. There were all transitions from simple proliferation of epithelium to obviously

autonomous atypical and pleomorphous growth of epithelium which highly probably had settled down by desquamation in the recess of Douglas and here gave origin to large tumurous plaque.

If already the circumscribed granular deposition of iron pigment pointed to presence of asbestos dust in the tumorous tissue on basis of similarity to those depositions in asbestotic fibrosis and in connection with Behren's experiments, this assumption was confirmed by rentgenographic finding of small amount of asbestos in the tissue of the tumor.

Nothing definite can be said about the way by which the detected asbestos dust reached the abdominal cavity. Theoretically, on basis of finding of asbestos bodies bodies in lung-root lymph-nodes and in the spleen, one must take into consideration possibility of transport by lymph- and blood circulation. The latter may be rejected in view of small deposition in the spleen and of improbability of any meaningful movement of long asbestos fibres through blood stream. Also lymphatic transport of asbestos from the lungs over the upper-abdominal lymphnodes, which regularly occurs according to our own investigations in silicosis, has only slight chance of realisation.

The highest probability belongs to assumption of direct piercing of asbestos fibres from the lung through the pleura. and later through the diaphragm, first of all because also the right diaphragm was strongly tumorously changed. Capability of asbestos fibres to penetrate the pleura may be considered proven by deposition in the pleura reported by Wedler. This obviously is the cause of in asbestosis regularly present pleural changes with exfoliation of epithelium, deposition of fibrin, adhesions and formation of plaques, and also of primary tumors of the pleura considering proof of asbestosis bodies in the tumor tissue as successfully made in the Weiss' case. Therefore in the case under discussion it may be with good reason assumed that also the diaphragm was penetrated by asbestos needles and that by this direct way small amount of the inhaled dust reached the abdominal cavity. Since in 1947 occurred an exudative pleuritis with following formation of calcified pleural plaques it must be assumed that substantial deposition of asbestos dust in the abdominal cavity had taken place already prior to that time

With this, one comes very close to the known latent period between exposure to asbestos dust and development of lung carcinomas.

So the histological formation of mainly the villous-papillary and nodular parts of the tumor as well as the deposition of granular iron pigment, and particularly the rentgenographic proof of asbestos dust in the tumor tissue strongly testify in favor of causal relationship between deposition of asbestos in the abdominal cavity as consequence of an occupational disease and formation of a primary tumor of epithelium of the peritoneum, and that through chronic, mechanical-inflammatory irritation of the peritoneum by asbestos fibres which had penetrated from the pleural cavity.

Summary :

It is reported on a primary, villous-papillary, partly nodulary-plaqueforming tumor of peritoneal epithelium in an asbestos worker with approximately 26 years of exposure to dust and with medium severe pulmonary asbestosis who died of a tuberculous leptomeningitis with tuberculous caries of lumbar spine and with widespread scarring pulmonary tuberculosis. On basis of the histological structure of the tumor with its deposits of iron dust and on basis of rentgenographic proof of asbestos dust in the tumor tissue, causal relationship between the two diseases is accepted. Genesis of the tumor is attributed to overshooting phenomena of regeneration of the serosa exposed to chronic foreign-body irritation, in the sense of theories of Ribbert and of Fischer-Wasels.

Literature :

See the attached original.

Translated from German original :
PRIMARER DECKZELLENTUMOR DES BAUCHFELLS BEI ASBESTOSE.

Legenda of figures :

Fig. 1. Pulmonary asbestosis. Low power magnification.

Fig. 2. Asbestosis bodies in the lung.

Fig. 3. Asbestosis bodies and deposits of iron dust in the vicinity of a capsulary artery of the spleen.

Fig. 4. Peritoneal tumor on the bottom of the diaphragm.

Fig. 5. Peritoneal tumor in the recess of Douglas.

Fig. 6. Focus of micronodular tumor in the mesenterium. Low power magnification.

Fig. 7. Villous proliferation of the intestinal serosa.

Fig. 8. Proliferation of epithelium on a serous villus.

Fig. 9. Formation of cavities and myxomatous formations on nodules in mesenterium

Fig. 10. Pleomorphous proliferations of the epithelium of the recess of Douglas.