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MESOTHELIOMA PERITONEI IN ASBESTOSIS PULMONUM

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MESOTHELIOMA PERITONEI IN ASBESTOSIS PULMONUM

[Following is a translation of an article by M. Frenkel and H.de Jager in the Dutch-language periodical Jaarboek van Kankeronderzoek en Kankerbestrijding in Nederland (Yearbook of Cancer Research and the Fight Against Cancer in the Netherlands), No 11, 1961, pages 99-106.]

Introduction

In persons suffering from asbestosis, bronchocarcinoma is ten times as frequent as in a comparable age group of the population as a whole (1). This observation has led to the assumption of a causal relationship between asbestosis and bronchocarcinoma in such cases. The recent literature also contains indications that other tumors, too, may occur more frequently in connection with asbestosis. A relationship with asbestosis has come to light especially in the case of the relatively rare mesotheliomata of the pleura, certain tumors of the ovaries, and the very rare mesotheliomata of the peritoneum. We shall describe the case of an insulator under our observation with a mesothelioma of the peritoneum.

Clinical History

The patient, a 46-year-old insulator, had worked with asbestos from the age of 16. In his work he sometimes had to strip old insulating material from pipes, -- a very dusty job. Nevertheless, the patient hardly ever coughed, though he did expectorate some thin mucus in the mornings. He had been

subjected to X-ray examination a few times, and no abnormalities ever showed up in the lungs. From his youth he smoked a pack of cigarettes a day. Until July 1960 he was completely well. At that time he noticed that his belly had grown fat in the course of a few weeks. Admission to Prof. A. Kummer's surgical section at the Binnen-Gasthuis /hospital for internal medicine/ at Amsterdam followed.

There was a hard tumor that could be felt in the lower abdomen and the abdomen was bloated. When a laparotomy was performed 5 liters of ascitic fluid was found and numerous tumors of varying size were observed on the parietal and visceral peritoneum. Dr. R. van Dam, pathologist and anatomist of the Binnen-Gasthuis, made the diagnosis: mesothelioma peritonei.

In December 1960 the patient, who in the meantime had been bothered by pain and increasing swelling of the abdomen, was admitted to Antoni van Leeuwenhoek House for palliative radiation treatment. Upon examination it was found that the patient was emaciated and had a grayish brown pigmentation of the skin, especially localized on the forehead, belly, and genitals and in the lines of the palm of the hand. This pigmentation first suggested the idea of Addison's disease. But no pigmentation of the mucous membrane was found and the blood pressure was practically normal: 130/90 mm Hg. The mineral spectrum too (sodium 135.5 m eq/L, potassium 4.8 m eq/L, chloride 86 m eq/L, and bicarbonate 30.4 m eq/L) was more in agreement with loss of chloride as a result of vomiting than with adrenal insufficiency. No abnormalities were found in the lungs either by physical or by X-ray examination. Mr. de Bourgraaf did find in the sputum bodies that looked like asbestos fibers, but no tumor cells. The abdomen was much bloated and contained ascites as well as several large tumorous masses.

In the urine, whose specific gravity as a result of dehydration was 1036, neither albumen nor glucose was found. There was a slight urobilinuria. In the sediment a few white but no red blood corpuscles were seen. The sedimentation amounted to 67 mm and the hemoglobin content only 9.4 gr %. The white blood picture (leucocytes 9900/mm³, cells with rod nuclei 3%, with segmented nuclei 82%, lymphocytes 15%) was practically normal.

The patient died of cachexia. The clinical diagnosis ran: mesothelioma peritonei in connection with (latent) asbestosis of the lungs.

Summary of Autopsy Findings (S. 31114)

The body was moderately well nourished. The skin had a brown pigmentation; the skin of the lower abdomen exhibited a brownish black color as a result of local radiation. In the abdominal cavity, separated into compartments, was found two liters of light yellow, somewhat viscous fluid. The entire peritoneum was covered with grayish white, somewhat slimy, soli tumor tissue, which on the intestines formed a layer up to 1 cm thick (Figure 1). Above and behind the bladder were found tumorous masses as big as the fist, containing cysts filled with yellow, viscous fluid. The gastrocolic omentum was also converted into a tumorous slab, while liver, spleen, and stomach were covered with a thick tumorous layer.

When the intestinal track was cut open it was found that the mucous membrane was intact. Tumorous foci were found superficially in the liver, the impression being that they had been formed by growth from the outside. (Figure 1.) No indication was to be found in the abdominal or pelvic organs that the tumorous process had originated outside the peritoneal cavity. Metastases were found in para-aortal lymph glands and in the lymph glands of the small pelvis and of the loins.

In the left pleural cavity was found 1 liter of yellowish brown, somewhat cloudy fluid, while the base of the left lower lobe was poorly developed. There were no growths on the left. In the right pleural cavity there was practically no

fluid; on the lower right there were a few growths between the layers of the pleura. The lungs weighed 1500 grams, felt a little firmer than normal, and were also slightly emphysematous. The pleura was thickened just a trifle (Figure 1). The incision into the lungs met some resistance. The surface of the cut was grayish red with a slight brownish tinge and showed numerous small black flecks. At the bifurcation of the trachea a couple of lymph glands were found that were largely taken up with tumor. The branches of the bronchial tubes were cut open peripherally a long way and no abnormalities were found. The diaphragm showed hyaline inspissations on the upper surface left and right. No tumor tissue could be detected macroscopically. The heart weighed 260 grams and showed no abnormalities.

Microscopic Examination

The tumor tissue from the abdominal cavity is made up of medium-sized, moderately polymorphous, cutical to flat cells, often covered with irregular fissures (Figure 2). There is infiltrating growth, among other places, in the diaphragm, a single tumorous spot being found on the upper side of the diaphragm. The metastases in the lymph glands show the same picture as the tumor tissue in the abdominal cavity.

The lungs show a moderate emphysema and numerous foci of fibrosis, with here and there larger areas of fibrosis, in which are found numerous cells laden with carbon and iron pigment and also dumbbell or club-shaped bodies with indentations like strings of beads (asbestos bodies). (Figure 3.) There are also smaller fibers, often birefringent. In the alveoli are found many cells laden with carbon and iron pigment, while asbestos fibers are also found free in the alveoli and in places without fibrosis. The pleura is slightly fibrous; the epithelial cells of the pleura show moderate to decided polymorphism (Figure 4) and in some cases are somewhat proliferative, being then indistinguishable from the tumor (Figure 5),

while basally, on the right, in lymph glands of the pleura, cells are found which are certainly to be interpreted as tumor cells (Figure 6). In the larger and smaller branches of the bronchial tubes metaplasia and polymorphism of the epithelium are detectable here and there, while scattered about the lungs foci are found, as a rule only a few alveoli in size, where polymorphous cells cover alveolar walls (Figure 7). The cell type thus coincides with that of the tumor in the abdominal cavity. These foci are not specifically restricted to places where asbestos bodies are found. No large tumor foci are found in the lungs. In one single lung hilus gland an asbestos body is found. Elsewhere in the body, namely in the spleen, liver, abdominal lymph glands, and tumor tissue in the abdominal cavity, no asbestos bodies or fibers are seen, but one is struck by the pronounced hemosiderosis of the spleen and the depositing of iron in Kupffer cells of the liver. The patient's skin unfortunately was not examined; possibly the brown pigmentation is also attributable to siderosis.

Discussion

Both from the preventive and the social point of view it is important if a malignant tumor is recognized as an occupational disease. What is the connection between mesothelioma and asbestos? A brief digression on asbestos is in place here (1,2).

The ancients were acquainted with asbestos, a collective name for a group of minerals with long flexible fibers which lend themselves to spinning and weaving and are completely non-combustible. The Greeks made wicks of this material for the oil lamps in their temples, and Herodotus mentions that the winding sheets for the bodies of rich persons were non-combustible so as not to contaminate the ashes of the dead with the ash of sheep's wool. Pliny the Younger is said to have reported that slaves got sick from working with asbestos. The legend is told of both Charlemagne and Charles V that in order to make an impression on his guests the emperor threw the table cloth into the blazing fireplace and had it pulled out undamaged. It is evident that the reference is to asbestos, which in those days was as costly as "the pearls of India."

Although the first recognized case of asbestosis of the lungs dates from 1900 (1), the danger from asbestos dust was not generally recognized until about 1930 both by the social security authorities and by those responsible for safety in factories and workshops.

The chemical composition of asbestos differs with the place where it is found. The most important components are Si, Fe, Mg, and Ca. During the nineteenth century the use of asbestos increased greatly. Great deposits of asbestos were discovered in Canada and South Africa. The present uses of asbestos are legion; one need only think of the concept "eternite" and of friction plates and brakeshoes in automobiles.

Asbestosis of the lungs is a serious disease, which sometimes results in death in 5 to 10 years with symptoms of shortness of breath, cyanosis, and insufficiency of the right ventricle of the heart. Diagnosis is based on the occupational record (the contact with asbestos is sometimes very brief), the distinctive X-ray picture with spotted, striped shading in the lower areas of the lungs, and the finding of asbestos bodies in the sputum. These are asbestos fibers covered with a layer of protein containing iron, which stains with Prussian blue.

In about 13% of asbestosis patients painful "asbestos warts" occur in the palm of the hand. Asbestos fibers are found in these warts. In one isolated case malignant degeneration of such a wart has been observed.

Sometimes a grayish brown pigmentation of the skin is reported, the nature of which has not been determined.

But there also seem to be numerous asymptomatic cases.

Gloyne in 1933 described the first case of bronchocarcinoma in connection with asbestosis (2). In 1942 Kampe reported the first Dutch case (3). The latent period elapsing between the first contact with asbestos and the bronchocarcinoma averages 23 years (1).

In scattered publications that concerned themselves with this aspect of asbestosis, besides bronchocarcinoma cases of mesothelioma pleurae have also been reported. Van der Schoot

in 1958 devoted an article to mesothelioma pleurae in asbestosis (4). In an article by Wagner et al. (5), 45 cases are described which the authors observed within a short time in connection with asbestos contacts in the mining district of South Africa. The average latent period between first contact and the tumor's becoming manifest is longer here than in the case of bronchocarcinoma, namely 20 to 40 years.

In 1954 the autopsy of an asbestos case was described by Leicher where the peritoneum was strewn with tumor tubercles that were considered to be a primary tumor of the peritoneum (6). No malignant processes were found in the lungs of the patient. Van der Schoot's paper on mesothelioma pleurae caused Schornagel to wonder whether a mesothelioma peritonei that he had observed in an insulator with asbestosis could be causally related to the asbestosis (4). Keal (7) reports a series of 30 patients with asbestosis who were admitted to The London Hospital and died there (15 women and 15 men). Fourteen of the patients had carcinoma of the lungs (10 men and 4 women). Nine women and one man had carcinoma of the ovaries or peritoneal tumors. In at least four of these cases the source of the tumors of the peritoneum cannot be sought in the ovary. No asbestos fibers could be found in the abdominal tumors. The latent period after the first contact with asbestos was longer in this group of abdominal tumors than in the case of bronchocarcinoma, namely more than 30 years. It is a striking fact that our patient, too, got sick 30 years after the beginning of his contact with asbestos. Wagner et al. (5) also reported among their large set of mesotheliomata pleura one case of mesothelioma peritonei.

It is difficult to imagine that the combination of asbestosis with mesothelioma peritonei, viewed in the light of the above-mentioned observations, is accidental. The question is in what way asbestosis after such a long latent period can

give rise to abdominal tumors. Are asbestos fibers transferred over a long period to the abdominal cavity, can it be that perhaps dissolved components of these fibers are carcinogenic at a distance, or is this simply a case of a very unusual type of metastasis of unrecognized bronchocarcinomata or mesotheliomata pleurae? In a few cases growth of a tumor of the pleura through the diaphragm has been observed. On the other hand in asbestosis asbestos fibers have been found in the spleen and in the abdominal lymph glands. Much more commonly asbestos fibers are present in the stools of asbestosis patients (from swallowing the sputum). It is conceivable that these microscopically thin needles can pass through the intestinal wall. In Leicher's case asbestos, although not visible with the microscope, was detected in the mesothelioma tissue with the X-ray spectrograph (6).

In our own case no asbestos bodies or fibers were found either in the abdominal cavity or in the liver or spleen. There was a growth through the diaphragm, the impression being that the penetration had taken place from below. In only one spot was tumor tissue, clearly recognizable microscopically as such, found on the upper side of the diaphragm. Tumor was also found in lymph glands of the pleura visceralis, on the lower right to be exact, and at the same time the covering mesothelium of the pleura showed decided polymorphism and here and there was also proliferative, so that differentiation from the tumor did not seem possible. Primary (or simultaneous) origin of the tumor process in the thoracic cavity could not be ruled out, although the macroscopic findings do not tell in favor of it.

In the lungs themselves foci were found where polymorphous cubical cells covered alveolar walls. Here too we were faced with a difficulty in interpreting these foci: were they of metastatic, primary, or simultaneous origin? The hemosiderosis of the liver and spleen (and possibly also of the skin)

could not be explained (connected with minute hemorrhages in the lung or with the iron from the asbestos fibers?).

Conclusion

From the literature it appears that when the air breathed is seriously contaminated with asbestos dust, a serious ventilative insufficiency may occur after 5 to 10 years, which sometimes results in death. Among the survivors after an average of 23 years there is a great chance of bronchocarcinoma, and after 20 to 40 years of mesothelioma of the pleura and/or peritoneum.

On the basis of these data we consider the connection between our patient's mesothelioma peritonei and his occupation (insulator) well-nigh certain.

This observation is another warning to get an accurate occupational anamnesis from patients with tumors.

Summary /Printed in English; slightly emended here./

A case is presented of a 46-year-old patient in whom in July 1960 a mesothelioma of the abdominal cavity was found. The man had worked for 30 years in an atmosphere contaminated with asbestos (insulation material). Neither clinically nor roentgenologically were there signs of asbestosis. The patient died half a year later.

At autopsy a grey-white tumor mass in the abdominal cavity covering the serosal layers was found (Figure 1) and two liters of slimy fluid. There was no primary tumor in the intestinal tract or in the other abdominal organs. There was ingrowth in the liver (Figure 1) and the diaphragm. In the left pleural cavity one liter of fluid was found and at the right lower side of the lungs there were adhesions between the pleural layers. There was some emphysema, anthracosis and fibrosis of the lungs and slight thickening of the visceral pleural layer (Figure 1). The parietal pleural layer of the diaphragm showed hyaline thickening but macroscopically no tumor growth. The bronchial tree did not show pathological lesions. In the retroperitoneal lymph nodes, in the inguinal lymph nodes, and in the hilar lymph nodes of the lung tumor deposits were found.

Microscopically the tumor tissue of the peritoneal cavity and of the lymph nodes was composed of pleomorphic flat or cuboideal cells forming clefts and tubules and sometimes papillary formations (Figure 2). There was infiltrating growth in the diaphragm among other places and microscopically small

tumorous foci were found at the upper side of the diaphragm. In the lung, besides fibrosis, emphysema, anthracosis, and cells laden with iron pigment, many asbestos bodies were found (Figure 3). The somewhat thickened pleural layer was covered in many places by pleomorphic cells (Figure 4), sometimes showing proliferation and then becoming indistinguishable from tumor cells (Figure 5). In a few lymph vessels of the pleural layer, namely at the right lower side, tumor cells were found (Figure 6). In the bronchial tree there were small areas of metaplasia and pleomorphism of cells, while in the lung tissue itself many foci were found in which alveolar septa were covered by pleomorphic cells of the same type as were found in the tumor tissue of the peritoneal cavity (Figure 7). These areas were not limited to areas with asbestos bodies. In most cases they involved only a few alveoli. Nowhere in the lungs were large tumors found. In one hilar lymph node of the lung an asbestos body was seen. Nowhere else in the other organs were asbestos bodies found.

A remarkable fact was the hemosiderosis of the spleen. Also, the Kupffer cells of the liver contained iron pigment. No microscopy of the skin, which showed a brown pigmentation, was done. Possibly this pigmentation was also caused by hemosiderosis.

To conclude, the combination of asbestosis of the lung and mesothelioma of the peritoneal cavity was observed. The macroscopic impression was that the peritoneal cavity was primarily involved. We could not, however, with certainty exclude a primary (or concomitant) involvement of the pleural cavity, and microscopically many small tumors were found in the lung. These could be explained as metastases of the peritoneal tumor or as primary (or concomitant?) tumors.

Referring to this case and the cases described in the literature it is concluded that the causal relationship between asbestosis and mesothelioma peritonei is very probable. The explanation, however, remains obscure.

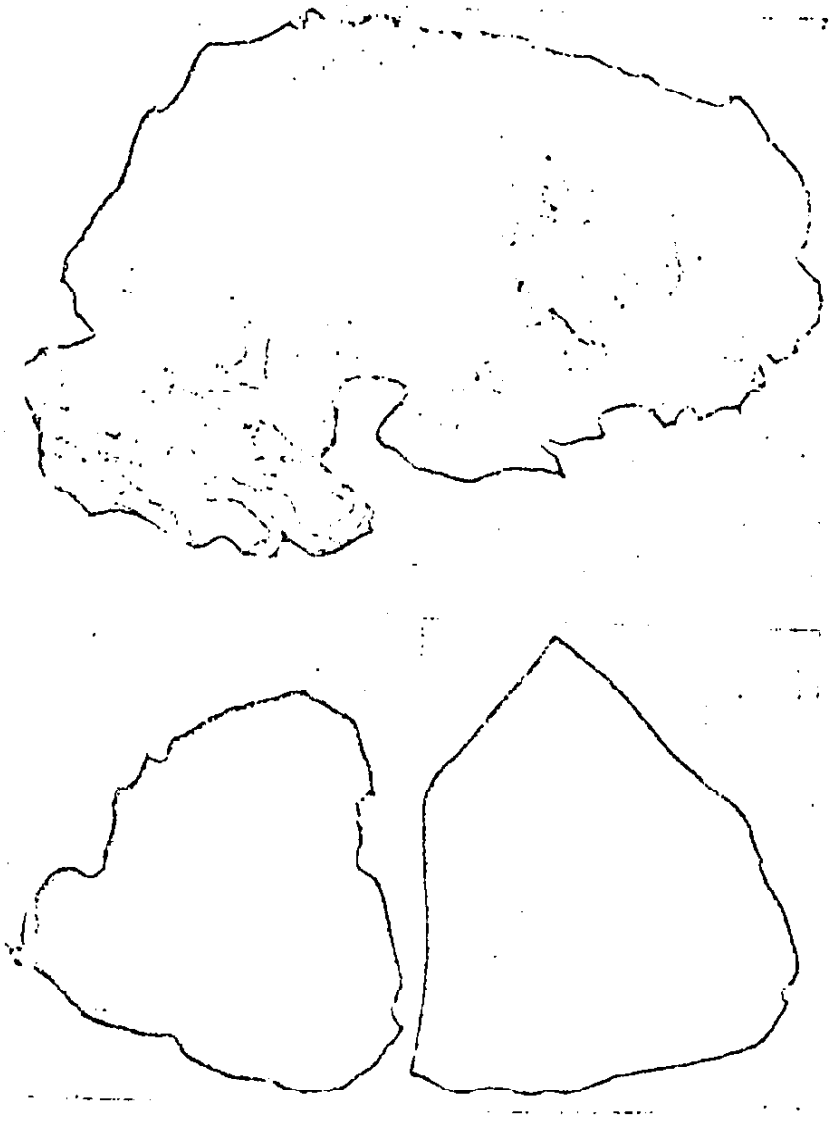

Figure 1. Top view of a bit of the serous membrane covering the intestine (cut open); cross section of the liver, and a bit of the serous membrane covering the small intestine + tumor; bit of lung with somewhat thickened pleura.

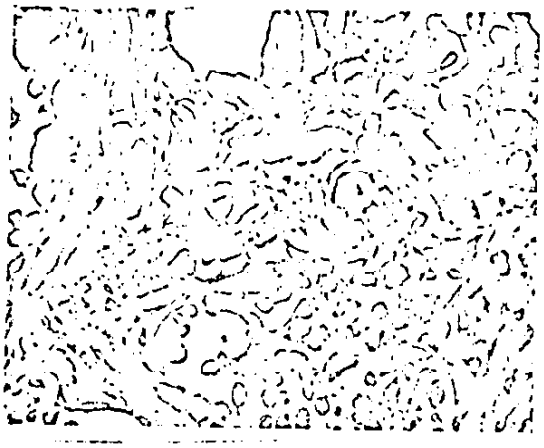

Figure 2
Microscopic picture of the tumor from the abdominal cavi

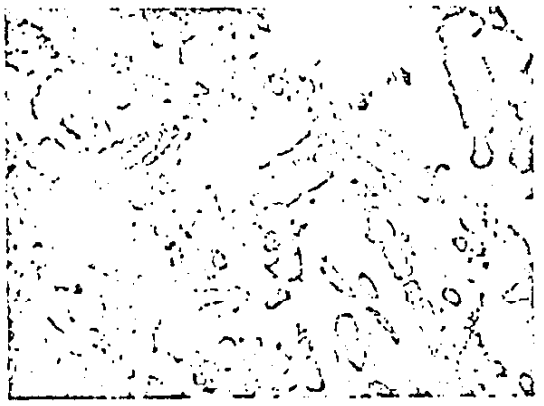

Figure 3
Lung with asbestos bodies.

Figure 4
Polymorphous pleura endothelio

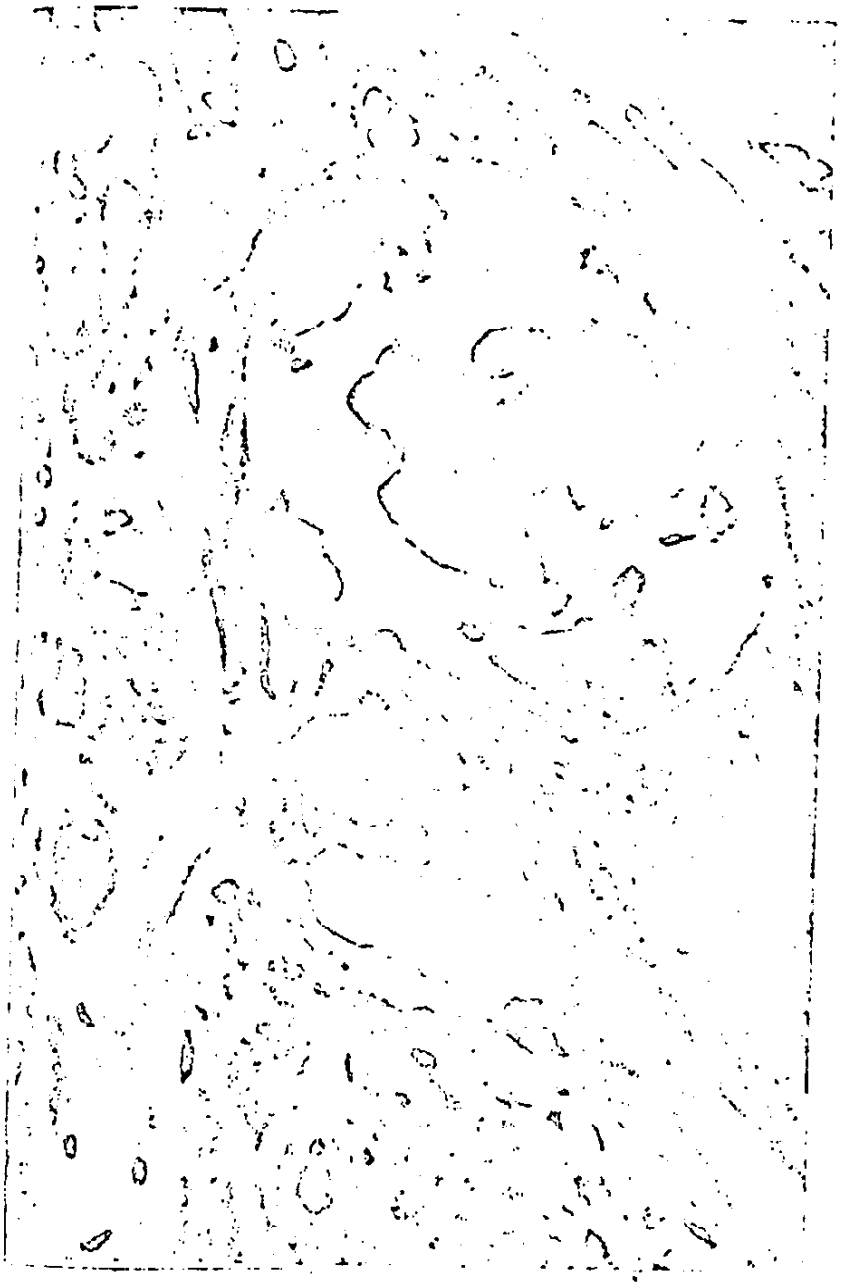

Figure 6. Tumor cells in lymph glands in the pleura visceralis.