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'Paraffinosis' secondary to bilateral oleothorax

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From the end of the last century (Hutchison, 1899) liquid paraffin was for several decades considered to be biologically inert, but such complications of its administration as lipoid pneumonia (Laughlen, 1925) and granuloma formation in lungs (Ikeda, 1937) and subcutaneous tissues (Lenormant and Ravaut, 1926) have shown it to be capable of producing an inflammatory response. We report a case in which oleothorax, induced as collapse therapy for pulmonary tuberculosis, gave rise to widespread lesions attributable to disseminated mineral oil.

CASE REPORT

This patient was aged 29 at the time of her death in May 1964. In 1951, at the age of 16, a diagnosis of bilateral pulmonary tuberculosis had been made. An artificial pneumothorax was induced on each side, and, because of difficulty in maintaining them, both were converted into oleothoraces, using liquid paraffin with crystalline penicillin in suspension. In June 1954 a relapse occurred on the left side which was treated with bed rest, streptomycin, and isoniazid for six months (Fig. 1). She made a good recovery and by 1955 was feeling well and started work.

Towards the end of 1956 she complained of morning nausea, malaise, and loss of weight, and in March 1957 she was referred for the first time to the London Hospital. Apart from the respiratory system, the most striking findings on physical examination were a palpable spleen three finger-breadths below the left costal margin and a slightly enlarged liver. The E.S.R. was 35 mm. in one hour (Westergren), haemoglobin 105%, and white blood count 4,600/c.mm. with a normal differential. A chest radiograph showed the presence of bilateral oleothoraces with a faint reticular shadow over both lower zones. A drill biopsy of the liver was done; liver function tests were normal. No satisfactory explanation for the splenic enlargement was found, and on the assumption that her symptoms might be due to a reactivation of tuberculous infection she was given chemotherapy. The patient herself stopped treatment after four months. She then complained of getting tired easily but of no other specific symptoms. On physical examination at this time not only was the splenic enlargement still present, but a palpable lymph node above the right clavicle was detected and a biopsy was taken. An attempt was made to remove the oil as completely as possible from both pleural cavities.

She remained reasonably well until February 1959, when she complained of listlessness and for the first time experienced breathlessness. She had lost about 6 lb. (2·7 kg.) in weight. The dyspnoea slowly got worse. In 1961 respiratory function studies showed that the vital capacity was reduced to about one-third of the expected value: pulmonary fibrosis and pleural thickening were thought to be the cause of this. Partially reversible airways obstruction was present. Breathing was fast and shallow, the efficiency of gas exchange was severely impaired (fractional carbon monoxide uptake 22%, arterial blood oxygen saturation 92·6% at rest, falling to 90·1% on exercise), and the patient was breathless on slight effort.

Her dyspnoea varied but continued slowly to progress until early in 1964, when she was admitted on account of right heart failure of subacute onset. A new physical finding on ophthalmoscopy was that of many small yellow spots over both fundi. She made a good recovery from the heart failure, but while convalescent developed a chest infection and died.

BIOPSIES Biopsy of the liver showed that fine vacuoles were present in many liver cells with focal coalescence of vacuoles, presumably fat-containing, in all parts of the specimen.

The microscopic appearance of a lymph node suggested a foreign body reaction to an extraneous oily substance. Large cyst-like spaces containing sudanophil material in frozen sections were surrounded by foreign body giant cells and dense fibrous tissue. Small foci of lymphocytes, representing the remnant of normal lymph node, were present.

NECROPSY Examination showed a wasted young woman with marked oedema of the legs. There was no clubbing.

Respiratory system The left pleural cavity was obliterated by firm white fibrous tissue up to 1 cm. thick, not penetrating the lung or interlobar fissures, and containing basal multiloculated cystic cavities filled with 30 ml. of clear yellowish oil.

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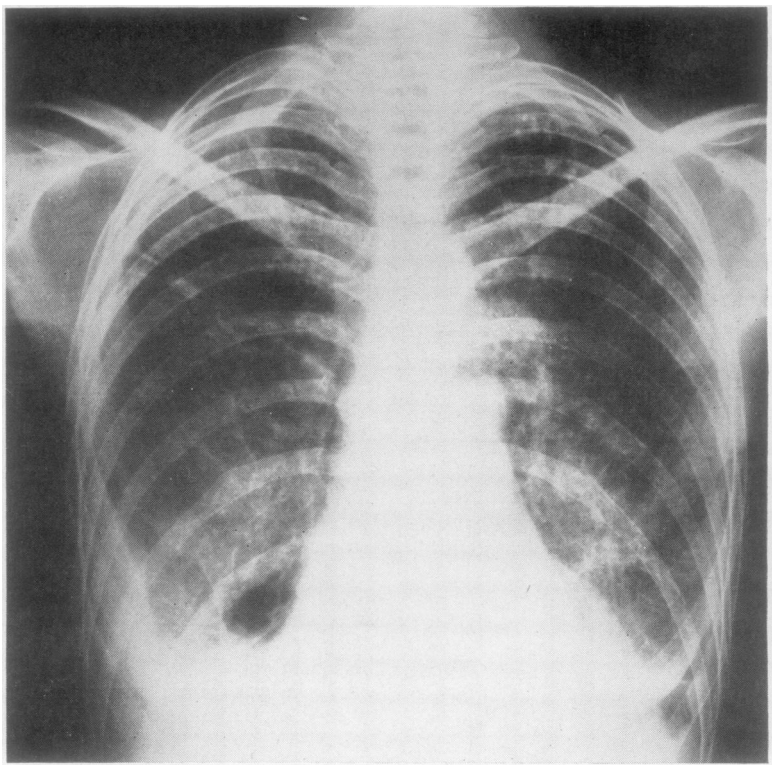

FIG. 1. *Chest radiograph taken one year before death shows encysted fluid at right base and small collection of fluid at left base. Diffuse mottling of lung fields is present, and there is a calcified lesion at the left apex.*

The right pleural sac was smooth and free of adhesions and contained six oil-filled loculi up to 2 cm. in diameter in the lower part of the paravertebral gutter. The superficial lymphatics of the right lung were visible as white subpleural streaks. Before fixation the parenchyma of both lungs showed a uniform pattern of miliary, fixed, creamy-white dots lying between air spaces; after fixation of the left lung sagittal slices 1 cm. thick were cut, revealing the pattern of honeycomb lung (Fig. 2), with air spaces averaging 0·3 cm. and up to 0·8 cm. in diameter. The apical segment of the left upper lobe showed coarse scarring with calcified foci up to 0·5 cm. across but no cavities. Similar calcification was present in the right middle lobe beneath the pleura. No atheroma was seen in the pulmonary arteries. The trachea and main bronchi appeared normal.

Reticulo-endothelial system On both sides, in the supraclavicular, lower deep cervical, and hilar groups, lymph nodes were enlarged up to 1·5 cm. in diameter; they were matted together and had coarse cystic cut surfaces from which oil exuded. Similar changes were present in the left gastric coeliac and mesenteric groups, but the axillary, portal, and inguinal nodes appeared normal. The soft enlarged spleen (465 g.) had a congested cut surface with inconspicuous Malpighian bodies.

Other organs The liver was enlarged (1,538 g.) with miliary, pale yellow, subcapsular spots on the superior surface. The cut surface showed a normal pattern with many similar pinpoint areas in portal tracts throughout the organ, sometimes with fibrosis most marked in the subcapsular region. The stomach and intestines appeared normal; no lesions were seen in the intestinal lymphoid tissue. The peritoneum was normal. The heart weighed 268 g. The thickness of the right ventricle was increased to 0·7 cm. in the outflow tract. The left ventricle was normal and the foramen ovale was closed. The kidneys, genital organs, and endocrine glands appeared normal. The brain was not examined.

MICROSCOPY Many of the tissues examined contained oil-filled spaces of varying size surrounded by macrophages and fibrous tissue.

In the lungs the architecture of the left lower lobe had largely been replaced by emphysematous cavities, many circular spaces enclosed by collagen and foamy

FIG. 2. *Left lower lobe of the lung at necropsy. Coarse trabeculation of parenchyma.* ×2·5.

macrophages, and smaller areas filled with similar vacuolated cells. Some areas showed bronchopneumonia. The circular spaces and foamy macrophages contained material staining red with Sudan III in frozen sections, which was not stained by Sudan black or osmic acid and did not fluoresce in ultraviolet light. The overlying pleura was greatly thickened by dense collagenous tissue containing similar staining oil droplets and macrophages. In the upper lobe the architecture was better preserved, although similar changes were present. A few subpleural arteries showed a thickened muscular intima with elastification, and there was also intimal thickening in the veins. No active tuberculosis was seen.

The normal structure of affected lymph nodes had been replaced by a coarse network of fibrous tissue containing macrophages, multinucleate giant cells, and a few small aggregates of lymphocytes surrounding small circular cavities (Fig. 3). The cavities and macrophages contained sudanophilic material as in the lungs. No germinal centres were seen.

In the liver large oil globules were present in the portal tracts with macrophages and excess fibrous tissue. The lesions in the spleen were mainly in the red pulp. They contained occasional giant cells and lipid globules.

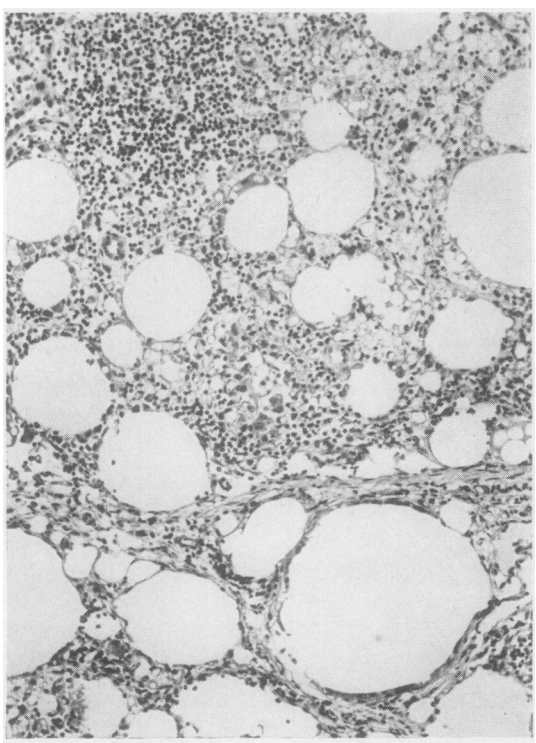

FIG. 3. *Lymph node. 'Swiss cheese' appearance. H.E.* × 120.

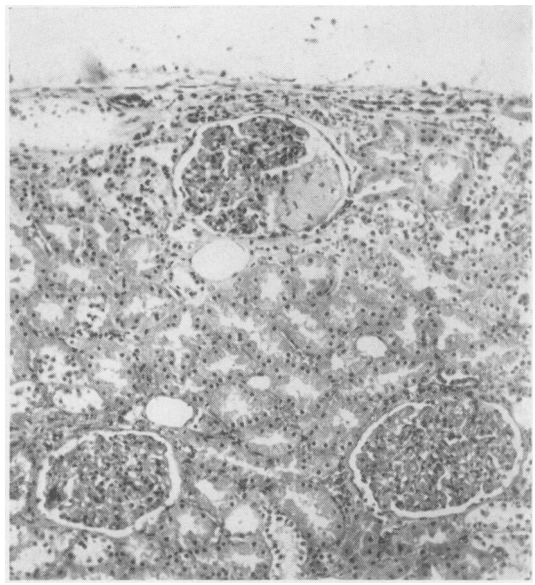

FIG. 4. *Kidney. Partly hyalinized glomerulus and interstitial oil spaces. H.E.* × 110.

The kidneys showed widespread diffuse thickening of the parietal basement membrane of Bowman's capsule in many glomeruli with lobular or rarely complete hyalinization of scattered glomeruli (Fig. 4). These lobular hyaline masses stained orange and purple with phosphotungstic acid-haematoxylin, were yellow-brown by the van Gieson technique, and weak pink or unstained with the periodic acid-Schiff method. Many interstitial oil droplets were seen and there were occasional fat globules in glomerular capillaries and in tubular epithelial cells. The interstitial lesions were mainly in the cortex. The interstitial tissues of both atria and ventricles contained many oil-filled spaces surrounded by macrophages; less frequent were smaller lesions consisting of groups of macrophages arranged about a hyaline, eosinophilic centre resembling Aschoff nodes (Fig. 5). Intermediate stages were seen between the two types of lesion. Groups of oil-containing macrophages were present in the thyroid, adrenals, ovary, tongue muscle, pectoralis major, and lymphoid tissue of the appendix.

DISCUSSION

Chemical analysis of the oil disseminated throughout the organs of this patient was not carried out, because it would have required gas-liquid chromatography or infra-red spectrography to give conclusive results, and these facilities were not available. In its pink staining with Sudan III, the failure to stain with Sudan black or osmic acid, and the lack of fluorescence, this oil

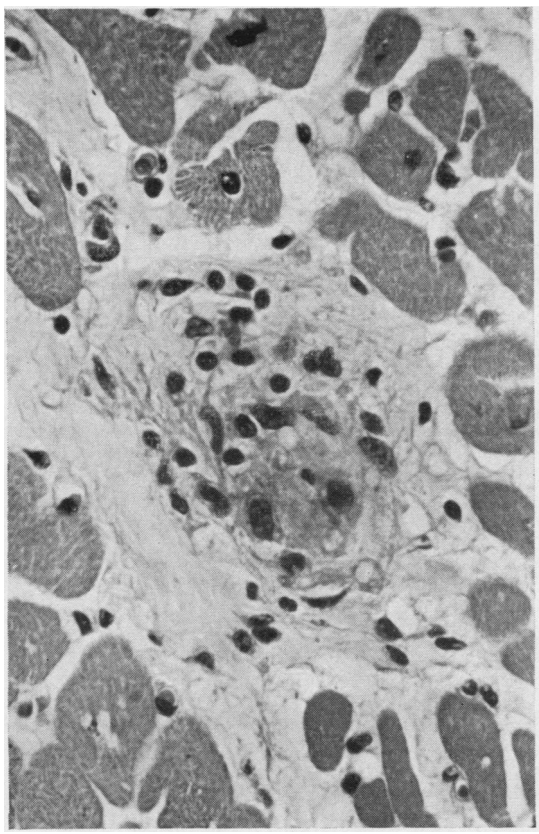

FIG. 5. *Heart. Interstitial granuloma in myocardium of left ventricle. H.E.* × 480.

resembled the liquid paraffin injected into the pleural cavities 13 years before death. Long-term sequelae of the intrathoracic administration of paraffin have been described infrequently, and this form of collapse therapy for pulmonary tuberculosis has been employed until recently. Such studies as those of Adams and Fritz (1952) showed the absence of complications in the first year, and Gaensler and Strieder (1951) measured the vital capacity, tidal volume, and residual volume in a patient with post-pneumonectomy oleothorax and found no deterioration of lung function in two years. The best documented sequel is the formation of mediastinal granulomata following oleothorax, extrapleural oil or extrapleural paraffin wax plombage, which appears to have similar effects ; such granulomata may constrict the oesophagus, produce dysphagia, and clinically may mimic oesophageal carcinoma. Kergin (1953) reported a case in which this occurred six years after the introduction of oil into the extrapleural space, and the regional lymph nodes showed the same coarsely, irregularly vacuolated, and fibrous 'Swiss cheese' appearance as in the present case. Toussaint and Toussaint (1949) reported three patients with paraffinomas after oleothorax, two of whom developed oesophageal obstruction after seven and 18 years. Another report is that of Moritz and Busanny-Caspari (1951). Of three cases described by Ballantyne, Clagett, and McDonald (1952) one became dysphagic four and a half years after treatment and a second had had an oleothorax 17 years before granulomatous involvement of the brachial plexus. The third suffered leakage of oil through the chest wall and developed an inflammatory mass in the breast six years after the introduction of paraffin into the pleural sac. Migration of oil is a well-recognized complication and may occur around the site of injection, with granuloma formation (Matson, 1932), or through other parts of the chest wall or the mediastinum, resulting in subclavicular or pectoral masses and involvement of the pericardium and the contralateral pleural sac (Livieratos, 1936). Bronchopleural and pleurocutaneous fistulae occurred in the cases of McBurney, Jamplis, and Hedberg (1955) two to eight years after oleothorax ; passage of oil into the lungs resulted in pneumonic changes, both acute and chronic, as described by Matson (1932). Prolonged exposure of the pleura to mineral oil, as in oleothorax, leads to fibrous thickening (Herbut and Charr, 1944) like that seen in the present case.

Widespread dissemination of inert mineral oil in one patient has not previously been reported, although most organs, with the notable exceptions of the heart and kidney, may be involved in certain circumstances: the renal lesions described in a case of lipoid pneumonia by Young, Applebaum, and Wasserman (1939) appear to be of an arteritic nature. Rabbits fed with paraffin-impregnated food for more than seven months were found to have white nodules 1 mm. in diameter in the jejunum, mesenteric lymph nodes, and liver, and rats showed similar involvement of the lymph nodes and had yellow flecks in the liver 'distributed according to the location of the portal tracts' (Stryker, 1941). Microscopically these lesions were composed of vacuolated cells, and in the lymph nodes the peripheral sinuses were difficult to recognize, while 'germinal centres' were distended with large vacuolated cells and extracellular vacuoles of varying size. The liver contained scattered irregular vacuolated lesions adjacent to the portal tracts and replacing the

parenchyma, and nests of vacuolated cells were also seen in the spleen. Stryker found similar lesions in the liver, spleen, and mesenteric lymph nodes of two patients who received by mouth large quantities of liquid paraffin in their last months of life, and Pinkerton and Moragues (1940) and Goldberg and Saphir (1958) have described similar findings.

The sites and microscopic appearance of involved lymph nodes in the present case suggest a spread of oil through lymphatics, but quantities of paraffin must have entered the blood-stream to reach such organs as the heart and kidneys. Cardiac lymphatics lie in the endocardial and pericardial region (Gould, 1960) and their distribution could not account for the spread of oil which had produced lesions through the full thickness of the muscle. In animals embolic hyaline lobular glomerular lesions may occur in anaphylaxis (Walter, Frank, and Irwin, 1961) and after intra-arterial injection of autolysed smooth muscle (Muirhead, Booth, and Montgomery, 1957). Cohnheim (1889–90) first observed renal oil droplets in experimental systemic fat embolism; Hagerty (1938) described focal endothelial proliferation around oil globules in the glomeruli of dogs after liquid paraffin injection into the renal artery, while Waaler (1943) showed in the kidney of a man who died of fat embolism four days after an accident both intraglomerular lipid and lobular hyaline lesions. It is therefore likely that the glomerular lesions in the present case represent a response to a paraffin embolus, while the number of renal lesions suggests embolism of moderate severity by comparison with cases of fat embolism following trauma (Sevitt, 1962). The absence of clinical cerebral manifestations is perhaps surprising, but may be related to the size and number of the emboli. The mode of spread of the oil in the present case appears to have been two-fold: such organs as the heart, kidneys, ovary, thyroid, and skeletal muscle probably received oil droplets via their blood vessels, whereas involvement of the lung and lymph nodes could be explained by lymphatic permeation. Paraffin oil may first have escaped from the oleothorax through pleural lymphatics and subsequently entered the blood-stream via the thorax duct. Some visceral lesions may have been caused by absorption from the intestine of expectorated mineral oil, and spread within the lungs may have been partly through the bronchial tree.

Liquid paraffin produces a minimal inflammatory response, exciting mainly a histiocytic reaction and mild fibrosis (Lenormant and Ravaut, 1926). Such gross findings as lung destruction and acute oil pneumonia possibly result from superadded infection; this could have contributed to the severe lung damage seen in our case, which was far worse than the lesions seen in other organs.

SUMMARY

A case is reported of 'paraffinosis' with widespread lesions due to mineral oil found at necropsy in a 29-year-old woman 13 years after oleothorax for pulmonary tuberculosis. The lungs presented a honeycomb picture, and granulomatous lesions were present in many tissues.

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