Lymphangiography in Hodgkin's Disease: Indications and Contraindications

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Summary

Lymphangiography is an invaluable tool for the detection of retroperitoneal lymphoma, and helps determine prognosis, since prognosis varies with clinical extent of disease.

Patients with Stage I and IIA Hodgkin's disease should have a lymphangiogram in order to definitely determine whether disease exists below the diaphragm in the retroperitoneal space. If disease is found, current evidence indicates that it should be treated with radiation therapy. Lymphangiography is usually not indicated in patients with Stages IIB and III disease. Retroperitoneal disease almost invariably exists and the procedure should only be done for specific indications. The contraindications of this procedure should be kept in mind and carefully scrutinized in every patient who undergoes the procedure. The error in interpretation of lymphangiogram films is at least 10%, and may well be higher, especially in inexperienced hands. Errors are almost invariably falsely negative readings, not false positives.

The value of uncovering occult asymptomatic retroperitoneal Hodgkin's disease is still unknown. One would have to assume that, with our current therapeutic tools, the therapy of all apparent foci of disease is of value in patients with generalized Hodgkin's disease. We do not know that this is so. Although the lymphangiogram has given us a great deal of information about extent and patterns of disease in lymphoma, and has helped us with supportive management in symptomatic patients, we still do not know whether the therapy of asymptomatic nodes demonstrable on a lymphangiogram is of benefit to the patient.

Introduction

Hodgkin's disease may present in localized fashion in perhaps 25% of cases, in sharp contrast to lymphomas or reticulum cell sarcoma, which rarely appear to be limited to a single nodal site of origin (14). It has been proposed that it may be possible to cure Hodgkin's disease with the use of radiation therapy (3, 4, 8–10, 15). This concept has had a recent surge of interest stimulated by improved survival data in patients with clinically localized Hodgkin's disease treated with aggressive, high dose radiation therapy to affected nodes and contiguous node bearing areas. Assuming this is the case, that higher doses and larger ports will improve survival rates, then it would seem to be of maximal importance to uncover every vestige of occult disease and treat this disease with aggressive radiation therapy.

The rationale for the use of lymphangiography in Hodgkin's disease is 3-fold. First, in patients with apparently localized Hodgkin's disease, asymptomatic retroperitoneal node involvement can be discovered with great reliability (1, 13, 14, 17) and subsequently treated in hopes of cure. Second, involved retroperitoneal nodes can be delineated in patients with generalized disease, and treated in order to obtain local control of disease and symptoms. Third, prognosis varies with extent of disease (15) and patient management is facilitated if accurate extent of disease is known. It must be added that the usefulness of the lymphangiogram is only proportional to its reliability and accuracy as a diagnostic tool, and is inversely proportional to its complication rate. These factors will be discussed in detail.

Technic

Lymphangiography technic will not be discussed in this paper. Nothing can be added to previously published reports (11, 14, 16). Suffice it to say that lymphangiography in the most experienced hands can occasionally be a difficult procedure and is expensive and time consuming. For these reasons, plus the various complications to be discussed, the indications for the procedure and its usefulness must be carefully examined. It is, however, by far the most sensitive tool for documenting occult retroperitoneal lymphoma (14) short of laparotomy.

Results

Table 1 presents the results of lymphangiography in 192 patients with Hodgkin's disease.

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disease. Only one-third of patients with IIA disease have demonstrable occult retroperitoneal involvement.

Patients with Stage III Hodgkin's disease almost invariably have retroperitoneal involvement. This fact has led us to believe that lymphangiography is only rarely indicated when patients have clinically generalized Hodgkin's disease, especially since this is the group in whom serious complications of the procedure most frequently occur.

Eight patients were studied who had Hodgkin's disease clinically limited above the diaphragm but who had extranodal involvement, either of the lung or of the chest wall. These patients seem to form a separate clinical pattern with progressive local extranodal infiltration by their disease. Retroperitoneal involvement does not seem to be an invariable complication. The single important factor in these 8 patients that seemed to help predict whether retroperitoneal node involvement would exist was whether generalized symptoms were present, i.e., fever, sweats, or itching. Those patients who did not have generalized symptoms had negative lymphangiograms. Thus, these 8 patients have been grouped with our Stage II patients, A if asymptomatic, B if generalized symptoms were present.

Complications

Table 3 lists the major complications of lymphangiography. Ethiodized oil (Ethiodol) is the dye usually used to opacify the lymph nodes. This dye invariably gains entrance to the vascular system through multiple lymphaticovenous shunts (7, 18), and through the thoracic duct as it empties into the left subclavian vein. Thus, pulmonary oil embolization invariably occurs (2, 5, 12, 14) and usually can be visualized on a chest film immediately following the procedure. If too much oil is shunted into the pulmonary vasculature, or if dye is diverted into the lungs too rapidly, symptoms of pulmonary insufficiency will result. If prior underlying pulmonary disease is present and the dye cannot be quickly cleared from the pulmonary capillaries, the pulmonary insufficiency can become severe, and deaths have been reported (13, 14) (see case report). This is the principal reason that indications for lymphangiography must be carefully scrutinized. The technical details of the procedure must be supervised closely, i.e., prevention of too rapid injection or of too much Ethiodol. Adequate radiologic monitoring is mandatory as the dye ascends the lymphatic chains.

Table 4 lists the major contraindications to the procedure, and underlying pulmonary disease of any kind leads the list. The pulmonary disease need not be symptomatic. Pulmonary fibrosis secondary to previous radiation therapy can frequently not be seen on a chest film, nor is it symptomatic, yet patients with prior radiation to one or both lungs are poor risks for lymphangiography. Any impediment to clearance of the dye through the pulmonary capillaries renders the patient a distinct risk for the procedure.

It must be noted that the only patient in our series of patients with Hodgkin's disease who died subsequently to lymphangiography did not have apparent underlying pulmonary disease (see case report). He did, however, have Stage III disease with palpable involvement below the diaphragm and because of the excessive lymphaticovenous shunts in this type of patient, and subsequent likelihood of extensive embolization of dye, the procedure should not have been done in this patient. We know from experience that patients with Stage III disease almost invariably have retroperitoneal involvement, so that from a medical standpoint, lymphangiography is rarely indicated.
practical point of view, the procedure is rarely necessary if generalized disease is apparent.

We have seen, apart from this series, 2 other deaths attributable to lymphangiography in patients with lymphoma. Both these patients had advanced generalized disease at the time the procedure was done. They also had underlying pulmonary disease. Four other patients with lymphoma, 2 with Hodgkin's disease, had severe pulmonary insufficiency secondary to pulmonary oil embolism. None of these had preexistent pulmonary disease, but all had known generalized Hodgkin's disease at the time of the procedure. In retrospect, lymphangiography was unnecessary in every one of these patients.

We have seen an occasional erythematous skin reaction to the ethiodized oil. These cases have been self-limited and not severe. Only 1 of our patients with Hodgkin's disease had this complication. However, we would consider history of allergy to an iodine-containing dye a contraindication to the procedure.

Recently an anaphylactic death has been reported after the administration of Alphazurine 2G (6), the patent blue dye we have been using for the labeling of the lymphatics prior to the incision. No such allergic complication to the patent blue had been reported in the literature pertaining to lymphangiography. The patient who died in anaphylaxis had received 6 ml of a 10% solution i.v. We have found adequate labeling of lymphatic vessels with the use of 0.2 ml of a 10% solution of dye injected s.c. into each foot. Thus the dose and route of administration are markedly different. Many of the reports pertaining to technic of lymphangiography describe the use of far greater amounts of Alphazurine 2G dye than we have been using. It would seem wise to keep the dose of Alphazurine as low as possible and to avoid i.v. injection.

Local infections occasionally occur at the site of the cut-down but these have never been serious in our series of patients. Patients with edematous feet and patients who tend to be too active during the 2-3 days following the procedure are those in whom infections might be expected to develop.

Occasional fever occurs after the lymphangiogram but usually in those patients who have extensive retroperitoneal disease or who have an excessive amount of Ethiodol deposited in the lungs. This fever subsides without antibiotics and other specific treatment. If excessive dye does accumulate in the lungs and symptoms of pulmonary insufficiency or fever result, there is very little that can be done for the patient. Neither corticosteroids nor antibiotics are effective.

Occasionally pain occurs in involved nodes in the abdomen or pelvis following the procedure, but this also subsides within a few hr.

We have seen globules of amorphous material, presumably Ethiodol, in the glomeruli at autopsy on 3 occasions (see case report). Underlying renal disease and an elevated blood urea nitrogen (BUN) might well be considered a relative contraindication to lymphangiography. The patient reported did have underlying renal disease at the time the procedure was done, and he died with a rapidly rising BUN and renal failure. Another possible complication, not as yet reported, would be excessive embolization of Ethiodol to the brain. If an underlying right-to-left shunt exists within the heart, such as a patent foramen ovale, it would certainly represent a contraindication to the procedure since considerable embolization of dye would undoubtedly occur into the brain.

Discussion

With the above considerations in mind, we must outline those patients with Hodgkin's disease for whom lymphangiography is of importance despite the contraindications.

It is currently proposed that radical and aggressive radiation therapy to the diseased area and contiguous node-bearing groups is essential if we are to raise the 5- and 10-year cure rates in patients with localized disease (9, 15). Lymphangiography certainly seems indicated in Stage I patients with disease above the diaphragm, in order that retroperitoneal involvement can be hopefully ruled out. If nodal disease is found, it should be treated with radiation in an attempt to eradicate all known foci of disease. Current reports indicate that treatment of these occult diseased nodes will prolong survival (4, 9, 15).

We should continue to examine patients with Stage I groin disease since we have too few patients in our present series to draw totally valid conclusions about the necessity for the procedure, although all such patients studied to date have had retroperitoneal extension of their disease.

The validity of lymphangiography in patients with Stage I Hodgkin's disease may still, however, be open to question. We have only 1 laparotomy following lymphangiography in a patient with Stage I Hodgkin's disease presenting above the diaphragm. Surgical exploration in this case confirmed the negative lymphangiogram. We have surgical confirmation of our lymphangiography interpretation in 3 patients with Hodgkin's disease presenting as Stage I in the groin, and in 8 patients with Stage I lymphosarcoma and reticulum cell sarcoma presenting in the neck or groin. Thus, we have 12 patients with Stage I lymphoma who have had surgical confirmation of the lymphangiogram interpretation. However, if Hodgkin's disease presents clinically in a single locus above the diaphragm, dissemination may well be microscopic, or submicroscopic, and perhaps impossible to appreciate with a lymphangiogram.

Patients with Stage IIA disease should have lymphangiography performed. If retroperitoneal disease is discovered, as it is in one-third of such patients, this occult disease can be treated, just as in Stage I patients, with radiation therapy in an attempt to eradicate all known foci of disease. If the patient has a negative lymphangiogram, treatment can be limited to the upper body and we might expect that such a patient would have a better prognosis. This latter point has not as yet been proved, but preliminary follow-up data on our clinical IIA patients show that there is a sharp difference in quality of survival between patients with a negative lymphangiogram and those who had demonstrable disease and thus were dropped into Stage III. Of 22 patients with a negative lymphangiogram, who have been followed for at least 18 months, only 1 is dead and the majority of the rest are free of active disease. Of 13 patients with an abnormal lymphangiogram, followed for 18 months or more, 3 are dead and most of the others have recurrent symptomatic disease. More exact data will be forthcoming when length of follow-up and the number of patients in each group are both greater and thus more significant from a statistical point of view.

It is this group of patients with I and IIA disease in whom
most interesting observations relative to the usefulness of lymphangiography and prophylactic radiation therapy will evolve. Because of past variations in therapeutic approach some of these patients have had aggressive radiation therapy to all areas of nodal disease. Others have had symptomatic local radiation therapy only. Comparative survival data will be most interesting, and should help us decide whether aggressive radiation therapy is truly of benefit to patients with generalized Hodgkin's disease. We have been studying our patients for only 3 years, and valid survival data are not available at this point. The question that keeps arising is, "Does the discovery of asymptomatic retroperitoneal Hodgkin's disease, and its subsequent treatment with current modes of therapy, prolong survival?" The answer is probably "yes," but remains to be proven.

The indications for lymphangiography must be carefully scrutinized in patients with Stage IIB disease. Of these patients, 90% have retroperitoneal node involvement demonstrable by lymphangiogram alone. A lymphangiogram would seem to be necessary if an attempt is being made to eradicate and "cure" patients with generalized Hodgkin's disease by irradiation of all involved node-bearing areas. On the other hand, since 90% of these patients have retroperitoneal node disease, and since one assumes a certain error in the reading of lymphangiogram films, from a practical point of view one could omit the lymphangiogram and treat the retroperitoneal nodes of every patient presenting with Stage IIB disease. The argument here seems unresolved.

From the conservative point of view of the physician who is interested in the palliation of patients with generalized disease, the lymphangiogram can be of use in the accurate delineation of a radiation therapy port, such as in patients with pruritus in whom the active focus of disease had not been found, or in patients with an autoimmune hemolytic anemia, again in whom the active disease had not been demonstrated. There are other clinical problems in which the lymphangiogram can be of assistance, such as in the radiologic demonstration of retroperitoneal nodes as a probable cause of jaundice, or back pain. Response to therapy can also be observed by following changes in the opacified nodes on periodic films of the abdomen.

Patients with Stage III Hodgkin's disease seem to almost invariably have retroperitoneal node involvement. Although only 50% of our 57 cases (88%) had abnormal lymphangiograms, 6 of the 7 patients who had negative films had retroperitoneal disease visualized by intravenous pyelogram, inferior vena cavogram, or spine films. The 7th patient, who had a negative lymphangiogram, intravenous pyelogram, and inferior vena cavogram was autopsied and had no retroperitoneal disease at postmortem. An interesting figure can be obtained from these data. Six out of 57 patients had negative lymphangiograms and yet had retroperitoneal disease demonstrable by other methods. This gives us an error of at least 10% in the detection of retroperitoneal disease by lymphangiogram. When one considers that these are all patients with clinically generalized disease, one might well assume that the actual rate of error is far higher than this when one includes patients with early and microscopic spread of their disease. It also must be remembered that these films were read by physicians supposedly expert in the interpretation of the lymphangiogram. If inexperience is added to the rate of error in interpretation of these films, one might guess that close to 20% of lymphangiograms could be read incorrectly.

This tends to dispel an impression reported in an earlier paper that the rate of accuracy in lymphangiogram interpretation is close to 95% (14). It must be stressed that the great majority of errors are false negatives, and not false positives. We have recommended exploratory laparotomy in those patients with borderline films and have not to date confirmed a false positive reading.

There is no question but that lymphangiography has enormously expanded our ability to document retroperitoneal extent of lymphoma. There is, however, a large question as to whether this increased diagnostic ability has enabled us to do any more than merely further separate out those patients who have a better prognosis. We have not been able to show that the discovery of asymptomatic retroperitoneal node disease is of value in prolonging survival in a given patient, because we do not as yet know whether the radical radiotherapy of all diseased areas in patients with generalized Hodgkin's disease will prolong life.

A note should be added relative to the usefulness of lymphangiography as a therapeutic tool. Koehler et al. (12) have accurately calculated the varying distribution of Ethiodol in the organs of dogs after lymphangiography as the concentrations vary over the 17 days following the procedure. The data collected should be of extreme interest to those interested in endoluminal radiotherapy. The inescapable conclusion is that the treatment of retroperitoneal lymphoma via the lymphatic route is undesirable since, if adequate material is injected for the treatment of all periaortic disease, extensive spill into the lungs and other organs will result. Radiation tumor dose to treated nodes is also extremely variable and unpredictable, since node filling is rarely uniform or complete. External radiation, which enables accurate dose and field size calculations, seems preferable.

Case Report of Patient Who Died Subsequent to Lymphangiography

W. S., a 23-year-old white male, had Hodgkin's disease diagnosed from a right supraclavicular node biopsy in 1959. He received multiple courses of radiation therapy from 1959 to 1963 for recurrent nodes in the supraclavicular and mediastinal areas with good regression. He was well until October 1964, when he developed groin nodes, epigastric pain and fever and was found to have hepatosplenomegaly and questionably palpable periarticular masses. Admission urinalysis revealed 8-9 RBC and 3–4 WBC/HPF, granular casts, and 3+ proteinuria; no bacteria were seen in the centrifuged sediment. The Hb was 13.4 gm, Hct 41%, WBC 9600 (53 polys, 38 bands, 1 eosinophil, 4 monos, 2 lymphs, 1 atypical lymph, and 1 metamyelocyte). The BUN was 52, fasting blood sugar 102 (Folin-Wu), uric acid 8.0, BSP 46%, bilirubin 2.85 mg total (2.07 direct), SGOT 48 units, alkaline phosphatase 3.6 units (Bodansky), total protein 7.1 gm (4.7 gm albumin), and prothrombin time 23.8 sec.

A lymphangiogram revealed extensive intraabdominal lymph node involvement. Intravenous pyelography failed to visualize the kidneys. Chest x-ray was within normal limits. Forty-eight hr following lymphangiography the patient noted the gradual onset of progressive shortness of breath. Physical examination revealed a respiration of 45, 101°F temperature, 110/80 blood pressure, and pulse 150 and regular. The neck veins were dilated and there were rales at both bases. Chest X-ray revealed bi-
lateral patchy areas of soft infiltration in the lower lung fields and a reticular pattern in the upper fields. Repeat BUN was 102. The patient became progressively dyspneic, febrile to 106°F, and hypotensive, and died. Postmortem examination was obtained.

**Gross Findings at Autopsy**

**EXTERNAL APPEARANCE.** The body is that of a well-developed, well-nourished, 23-year-old white male who measures 75 inches in length and weighs an estimated 200 pounds. Livor mortis and rigor mortis is present. The head is normocephalic with a full growth of black hair. The pupils are equal bilaterally, measuring 4 mm. Icteric sclerae are noted with jaundiced skin. The nose, mouth and ears are unremarkable. No supraventricular lymphadenopathy is evident. The trachea appears to be in the midline. The thyroid is not palpable. There is a right supraclavicular scar measuring 5 cm. The chest is symmetrical. The abdomen is saepholial. Extremities are normal. The genitalia are those of an adult male.

**INCISION.** The usual Y-shaped incision is employed. On opening the peritoneal cavity the abdominal organs bear the usual relationship to each other. The liver extends 5 cm below the right costal margin. The spenic tip is palpable and extends 3 cm below the left costal margin. The diaphragms rise to the height of the 5th rib bilaterally.

**THORACIC CAVITY AND MEDIASTINUM.** The lungs occupy approximately 80% of the available space. There is approximately 25 ml of pleural fluid bilaterally which is cloudy and hemorrhagic. The pericardial cavity is opened and reveals 15 ml of clear fluid. The mediastinal lymph nodes are prominent, measuring up to 4 cm. They are soft and fluctuant. The thymus is not identified.

**HEART.** Weight 450 gm. The pulmonary artery is clear of emboli. The epicardium is smooth and glistening. The myocardium is red brown. The valve leaflets are grossly normal. The chordae tendineae are normal. The valves measure, in cm: mitral 10.5, aortic 7, tricuspid 13.5, pulmonary 8. The left ventricle measures 1.6 cm and the right 0.3 cm. The chambers of the heart are dilated with flattening of the epicardial surface. Coronary arteries are examined and are widely patent.

**AORTA, RENAL ARTERIES, AND VENA CAVA.** The aorta reveals an occasional minute plaque measuring up to 1 mm. The renal arteries are widely patent as is the inferior vena cava.

**LUNGS.** The right lung weighs 1450 gm, the left 1425 gm. The pleural surfaces are red-blue with overlying fibrinous material, especially the lower lobes bilaterally. On sectioning, the parenchyma is firm, red-blue in color, and hemorrhagtic fluid can be easily expressed. On inspection of the bronchi there is a hemorrhagic frothy material completely filling the lumina. The cortices measure 1 mm and are yellow, as are the underlying medullae.

**SPLEEN.** The spleen weighs 1425 gm. The surface is a mottled red-purple. On sectioning the parenchyma is softened with a deep red-brown appearance. Near the surface are several mottled areas of yellowish gray discoloration. There is no nodularity to the parenchymal surface.

**PANCREAS.** The pancreas weighs 115 gm. It is firm, yellow, tan and coarsely nodular. The pancreatic duct shows no evidence of dilation.

**ADRENALS.** The right adrenal weighs 10 gm, the left 12 gm. The organs are soft and somewhat edematous. The cortices measure 1 mm and are yellow, as are the underlying medullae.

**KIDNEYS.** The right kidney weighs 225 gm, the left 240 gm. The capsule strips with ease, revealing a smooth, red-brown, swollen surface. On sectioning, the cortex and medulla are well delineated. The cortices measure 7 mm in thickness. Near the pelvic papillae are areas of yellowish streaking. The pelvices are lined by a gray-white mucosa leading to the ureters which follow the normal course to the bladder. There is no evidence of extrinsic obstruction or dilation of the ureters.

**PELVIC ORGANS.** The bladder is opened anteriorly. The mucosa is somewhat edematous and has a greenish cast. The prostate and seminal vesicles are grossly normal. The testes are examined and appear grossly normal.

**GASTROINTESTINAL TRACT.** The esophagus and stomach are opened longitudinally. The esophagus mucosa is gray with some wrinkling of the mucosa. The stomach contains approximately 300 ml of greenish black bile. The rugal pattern is diminished. There is no evidence of bleeding points or injection. The duodenum is grossly normal. Small and large bowel are examined and are grossly normal.

**NECK ORGANS.** Trachea and larynx are opened posteriorly. There is an extensive amount of injection and the lumina are filled with a hemorrhagic frothy material. The thyroid is found in the usual paratracheal position. It weighs 18 gm. The lobes are homogeneous red-brown. Parathyroids are not identified.

**BONE MARROW.** The vertebrae are examined and the marrow appears light brown, somewhat pale, and without gross evidence of replacement by disease.

**LYMPH NODES.** There is extensive lymphadenopathy extending along the aorta, the paraesophageal area, along the esophagus within the mediastinum and in the hilus of the lungs. The nodes measure up to 4 cm and are soft and fluctuant. On sectioning they are yellow-brown.

**CRANIAL CAVITY.** The calvarium is removed. The dura is grossly normal. Brain weighs 1450 gm. On the ventral surface there is some mild uncalt herniation. The vessels follow the normal course and distribution. The brain stem and cerebellum are examined and are grossly normal. The brain is sectioned. The gray and white matter has a normal distribution as do the basal ganglia. The ventricular fluid is clear. The ventricles show no evidence of dilation. The pituitary is examined, removed from the sella turcica, and is grossly normal. The venous sinuses show no evidence of obstruction.

**Microscopic Findings**

Findings were not unusual in the heart, jejunum, and prostate. **LUNGS.** The lung sections reveal widespread pulmonary hemorrhage and pulmonary edema. Found throughout the dilated capillaries are numerous clear globules partially filled with dark brown material which did not polarize. This material is noted in the alveolar spaces.

**LIVER.** Sections of liver show marked acute cholangitis with a
polymorphonuclear infiltrate. Occasional brown globules are seen.

**Spleen.** There is postmortem change. The white pulp has undergone autolysis and numerous polymorphonuclears are present with autolyzed mononuclear cells and increased fibrosis. There is some brown debris present, which has a globular appearance.

**Pancreas.** There is postmortem necrosis.

**Lymph Nodes.** There is extensive postmortem autolysis with loss of nodal architecture and diffuse mononuclear cell infiltration.

**Kidneys.** There is marked postmortem autolysis. There are areas of interstitial hemorrhage. There is extensive brown, globular-appearing debris within the glomerular capillaries.

**Brain.** There is focal gliosis present in the cortex.

**Bone Marrow.** The marrow is cellular with increased megakaryocytes and a shift to the left in the white cell series.

**Final Anatomic Diagnosis**

1. Hodgkin's disease, clinical Stage III, involving spleen, thoracic and abdominal nodes.
2. Acute cholangiolitis; hepatomegaly.
3. Status 48 hr post lymphangiography with acute pulmonary edema and hemorrhage.
4. Cardiac dilation.

**Comment**

This 23-year-old man with a 5-year history of Hodgkin's disease came to the hospital with high fever. He was found to have abnormal liver chemistries, a high uric acid, and BUN. After a lymphangiogram these complaints progressed in severity. He developed acute respiratory distress and died in 48 hr.

Due to the prolonged postmortem interval, there is much autolysis and much less information is available than usual. The evidence for Hodgkin's is almost nonexistent microscopically owing to preferential autolysis of nodes and spleen. The liver shows well-established and extensive inflammation. Necrosis is not now separable from postmortem changes. The precise cause of the patient's renal disease could not be determined. The lymphangiographic dye is still recognizable and widespread. It is the most likely cause of the pulmonary pathology, but it seems probable that the liver disease was a major factor in the fatal outcome.

**References**

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