A female patient from Greece, born in 1955, visited our office in January 1998 for evaluation of recurrent right pleural effusion (Figure). The patient was treated for Hodgkin's disease (supra-clavicular and mediastinal lymph node enlargement) with radiation and chemotherapy in February 1974. The treatment consisted of a series of MOPP (nitrogen mustard, vincristine, procarbazine and, prednisone) and Co60 radiation over the mediastinum and lymph nodes above the diaphragm. Details about the radiation, including dosage, were not available. She also had a splenectomy at that time. The treatment of Hodgkin's disease was successful and led to disappearance of the enlarged lymph nodes. The patient felt well and was able to receive a degree from a graduate school and subsequently to work full-time without any problem.

The patient initially felt progressively short of breath during November 1997. She did not have any fever. A chest x-ray at that time showed bilateral pleural effusion and enlargement of the shadow of the heart. An echocardiogram revealed a significant amount of pericardial fluid. The patient was subsequently admitted to a hospital for treatment.

During a six-week inpatient stay she had an extensive work up for the etiology of the bilateral pleural effusion and pericardial effusion. A pleuritic fluid analysis showed specific gravity of 1.020, protein 4.6 gr/dL, glucose 98 mg/dL (within the range of normal values compared to serum glucose), and pH 7.5. Gram stain and stain for mycobacteria did not show the presence of microorganisms. Cultures of pleuritic fluid specimens for aerobic and anaerobic bacteria as well as mycobacteria were negative. An abdominal CT scan and a chest MRI did not show any lymph node enlargement. Erythrocyte sedimentation rate (ESR) was 56 mm/first hour. Hematocrit, white blood cell count, platelets, transaminases, alkaline phosphatase, ãGT, creatinine, blood urea, globulin, albumin, protein electrophoresis, electrolytes, urinalysis, â2-microglobulin and serological tests including hepatitis A, B, and C virus serology, VDRL, Widal and, Wright were normal. A tuberculin skin test was negative.

An extensive evaluation for an underlying collagen vascular or rheumatologic diseases that included tests for antinuclear antibodies, anti-DNA antibodies, lupus erythematosus cells, measurement of the third and fourth component of complement (C3 and C4), and a test for rheumatoid factor were normal.

The patient was given treatment with steroids for three weeks that did not lead to a considerable decrease of the amount of pericardial or pleural fluid. A trial with non-steroidal anti-inflammatory drugs was given for about one month (indomethacin 50 mg three times a day for 10 days and colchicine 1 mg twice a day for 20 days). No improvement was noted with this treatment either. She was transferred to another hospital where a biopsy of the pericardium was performed.

What is the most likely cause of the pericardial and pleural effusion?

Diagnosis
Pathology did not find any evidence for lymphoma, other neoplastic process, rheumatologic, or infectious disease; there was evidence for a chronic inflammatory reactive process. Specifically, increased connective tissue substrate was noted, with areas of intense hyalinization, a mild to moderate chronic inflammatory infiltration with deposits of hemosiderin, and hyperplasia of the mesothelial cells. These lesions were suggestive of a chronic fibroplastic pericarditis with elements of an old hemorrhage, more likely due to effects of radiation.

Differential diagnosis
Many neoplastic conditions, among of which are thoracic, pulmonary and ovarian cancer and, lymphomas can cause accumulation of fluid in the pleura. In view of the patient's history, the possibility of persistent pleural effusion related to recurrence of Hodgkin lymphoma or a new neoplastic process should have been strongly considered. However, the absence of convincing laboratory or imaging evidence for such a diagnosis and the fact that the process did not advance...
during the last seven years make this possibility less likely.

Teaching points
- Mediastinal radiotherapy can cause acute lung injury such as radiation pneumonitis, which typically occurs 2 weeks to 4 months after treatment and is usually limited to the irradiated field. Late post-radiation complications from the organs of the neck and chest include pericarditis, myocardial fibrosis, coronary artery disease, valvular abnormalities, conduction disturbances, pulmonary fibrosis, benign cysts of the thymus, esophageal carcinoma, recurrent laryngeal nerve paralysis, and thyroid dysfunction. In addition, fatigue seems to be one of the most frequently reported symptoms among long-term Hodgkin's disease survivors.
- The most likely cause for the pericardial and pleural effusions of this patient is late effect of radiation. Pericarditis may occur in an acute, subacute, and chronic form after mediastinal radiation therapy. In a study of 499 patients with all stages of Hodgkin's disease who received mediastinal irradiation, 9.5% had developed pericarditis after a period of ten years. Post-radiation pericarditis and pleuritis may occasionally appear very late after treatment for Hodgkin lymphoma. Pericarditis is frequently self-limiting and can occur acutely in 1% of patients given radiation treatment. The use of new imaging methods facilitates the accurate detection and management of complications such as pericardial effusion.
- The management of pleural effusion after radiation treatment is unclear. A possible therapy is pleurodesis (fusion of the visceral and parietal pleura) with a sclerosing agent. The substances preferably used for pleurodesis are, in the order of decreasing frequency of use, tetracycline, bleomycin, t alc, doxycycline or minocycline. Doxycycline can be injected in the pleural cavity (500 mg in a total volume of 50 ml), through a chest tube.

References

Acknowledgments
- The case was prepared for our website by Konstantinos N. Fragoulis, M.D.
- We thank Eleni Handrinou, M.D., Vasilis Papadopoulos, M.D., Konstantinos Dardoufas, M.D. and Tamamidou Maria, Ph.D. for their contribution in the care of the patient.