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Systemic Talc Granulomatosis Associated With Disseminated Histoplasmosis in a Drug Abuser

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• A 32-year-old intravenous drug abuser was found to have systemic talc granulomatosis and disseminated histoplasmosis. The clinicopathologic findings of this case support the hypothesis that the patient was predisposed to disseminated histoplasmosis by repeated intravenous talc administration. The effects of silica, a close relative of talc, on macrophages and the role of macrophages in recovery from *Histoplasma capsulatum* infection are described.

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Inhalation of *Histoplasma capsulatum* microconidia produces a pulmonary infection that is followed by a rapid, transient, hematogenous dissemination.[1] The infection is aborted with little or no symptoms in the majority of patients. Factors predisposing people to systemic disease include age extremes, hematologic malignancy, and iatrogenous or HIV-mediated immunosuppression.[2,3] In healing or healed primary histoplasmosis, degenerating fragments of the infecting organism are frequently observed within macrophages.[1] In contrast, one striking histologic feature of disseminated histoplasmosis is the lack of intracellular fungus destruction by macrophages. Thus, it appears that the inability of macrophages to kill *H capsulatum* is a key element leading to disseminated disease.[1]

We recently cared for an intravenous drug abuser with systemic talc granulomatosis and disseminated histoplasmosis. Obvious risk factors for disseminated histoplasmosis were lacking in this patient. Silica, which is closely related to talc, is known, however, to inhibit macrophage function.[4] We review the clinical and the pathologic features of this case and propose that talc predisposed the patient to disseminated histoplasmosis.

REPORT OF A CASE

A 32-year-old man was admitted to the Kansas City (Mo) Veterans Administration Medical Center with a fever of unknown duration. He admitted to alcohol abuse and he had been treated for narcolepsy for seven years with methylphenidate hydrochloride (Ritalin) tablets, but he denied use of nonprescribed drugs.

On admission, he was well developed, fairly well nourished, and in no acute distress, but he had a temperature of 37.5°C. Pertinent physical findings included hepatomegaly to 5 cm below the right costal arch, bilateral axillary lymphadenopathy, and 3+ pitting edema in both extremities. There were needle tracks, both new and scarred, bilaterally at the antecubital fossae. Ophthalmologic examination revealed tiny crystals in both retinas. The remaining physical findings were unremarkable.

Chest roentgenography showed multiple small densities in both lung fields. A urine drug screen was negative. Serum protein electrophoresis showed a polyclonal hypergammaglobulinemia. Relevant laboratory findings included: hemoglobin, 79 g/L (7.9 g/dL); white blood cell count, 9.3×10^9/L ($9300/mm^3$) (0.41 [41%] polymorphonuclear leukocytes, 0.24 [24%] lymphocytes, 0.24 [24%] atypical lymphocytes, 0.03 [3%] band cells, and 0.08 [8%] monocytes); aspartate aminotransferase, 305 IU; serum gamma-glutamyl transpeptidase, 124 IU; alanine aminotransferase, 60 IU; total serum bilirubin, 10 μmol/L (0.6 mg/dL); ethanol, (>29 mmol/L) 137 mg/dL; total serum protein, (89 g/L) 8.9 g/dL; albumin, (38 g/L) 3.8 g/dL; globulin, (510 mg/dL) 5.1 g/L; hepatitis B core antibody, positive; hepatitis B surface antigen and antibody, negative; and cytomegalovirus indirect immunofluorescence antibody titer, 1:512.

Histologic examination of a bone marrow biopsy specimen revealed multiple noncaseating granulomas of varying size.

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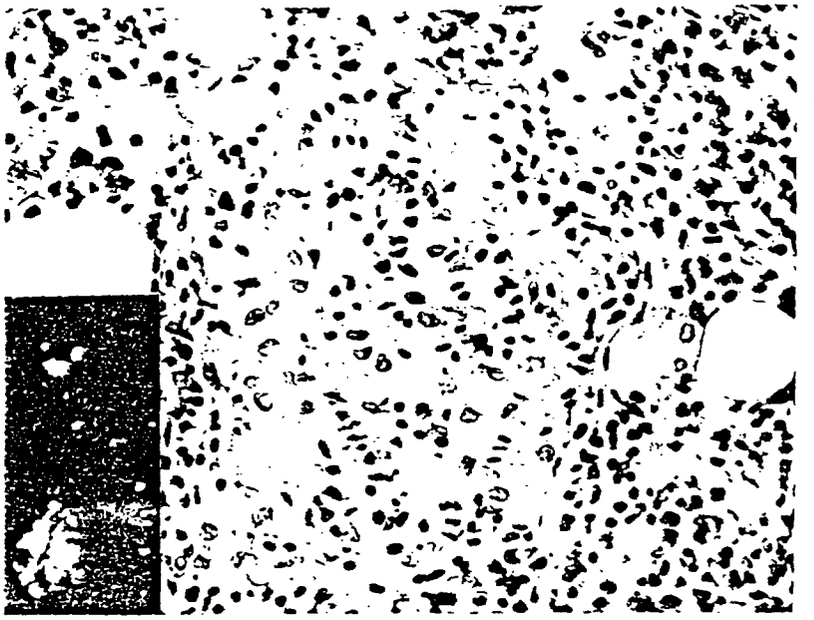

Fig 1.—Noncaseating bone marrow granuloma (hematoxylin-eosin, ×280). Inset, Polarization microscopy showing birefringent crystals in bone marrow granuloma (×280).

They consisted primarily of multinucleated giant and epithelioid cells surrounded by lymphocytes (Fig 1). Fibrosis was not noted in any of the bone marrow granulomas. Birefringent needle-shaped crystals varying from 1 to 2 μm in length were present within giant cells (Fig 1). A Grocott's methenamine silver stain revealed few intracellular yeasts within multinucleated giant cells (Fig 2). Viral inclusions were not noted, and viral cultures were negative. Culture of the bone marrow biopsy specimen produced *H capsulatum*. This identification was confirmed by production of tuberculate macroconidia at room temperature and conversion to the yeast phase at 37°C. A histoplasmin skin test induced a strongly positive response. Complement-fixing antibody titers to histoplasmin and yeast phase antigens were negative on initial presentation; follow-up tests were not performed.

A liver biopsy specimen showed chronic active hepatitis with portal and intralobular noncaseating granulomas containing the crystals described above, and occasional yeasts. Immunohistochemical peroxidase-antiperoxidase staining for hepatitis B surface antigen was negative. An axillary lymph node biopsy specimen showed no granuloma. There was, however, marked proliferation of sinus histiocytes, some of which contained melanin and the birefringent crystals described above. *Histoplasma capsulatum* was recovered from the lymph node biopsy cultures. Viral inclusions were not noted in either the lymph node or liver biopsy specimen and viral cultures of the lymph node were negative.

Electron microscopy of the bone marrow and the lymph node biopsy specimens revealed crystals in the cytoplasm of multinucleated giant cells and macrophages (Fig 3). These crystals most closely resembled talc.

In view of the patient's disseminated histoplasmosis and physical findings indicating intravenous drug use, peripheral T-cell subsets and T-cell function were assessed by flow cytometry and mitogen stimulation. At the time of these studies the total leukocyte count was 10×10^9/L (10 000/mm³); lymphocytes composed 0.57 (57%) 5.7×10^9/L (5700/mm³) of the total leukocytes. Total T-cells (T_{11}), T_{helper} (T_4), and $T_{suppressor}$ (T_8) cells composed 0.89 (89%) 5.1×10^9/L (5073/mm³), 0.31 (31.4%) 1.8×10^9/L (1790/mm³), and 0.51 (50.6%) 2.9×10^9/L (2884/mm³), respectively of the peripheral lymphocytes. The T_4/T_8 ratio was depressed (0.62) due to an increased number of suppressor cells; total T- and T_{helper}-cell numbers were within normal limits. The blastogenic responses to phytohemagglutinin and concanavalin A (Con A) was moderately decreased.

Intravenous therapy with amphotericin B was initiated, and continued until the patient received a total of 1.94 g. The *H capsulatum* infection was eradicated and the patient has survived for over three years, without recurrence, since completing his course of antifungal therapy.

COMMENT

Visceral granulomatosis is not uncommon in intravenous drug abusers. Granulomas occur most frequently in the lungs; however, intravenous drug abusers with hepatic and systemic granulomatosis have also been reported.[1] The granulomas form in response to particulate matter, usually talc, used as filler for pharmaceutical agents intended for oral but administered intravenously. Intravenous talc administration can also induce fibrotic, angiothrombotic, and hypertensive pulmonary changes, and may eventually lead to cardiorespiratory insufficiency and death.[2] Methadone hydrochloride, morphine sulfate, methylphenidate hydrochloride, tripelennamine hydrochloride, and propoxyphene hydrochloride are examples of pharmaceuticals commonly "cut" with talc for intravenous use.[3] Although the patient denied intravenous drug use, we assume that methylphenidate was administered intravenously because this agent is frequently cut with talc, has been associated with talc granulomas, was available to the patient, and the patient had physical signs of intravenous drug abuse. Use of other drugs could neither be substantiated nor refuted.

The affects of talc (magnesium silicate) on the immune system have not been well studied. Silica (silicon dioxide), which is closely related to talc, inhibits macrophage function and has been associated with an increased incidence and severity of infection due to *Mycobacterium tuberculosis*.[4] An increased incidence of tuberculosis is also seen in talc miners.[5]

Experimental mycobacterial infection is potentiated by silica injection or by inhalation of silica dust. Manifestations of experimental mycobacterial infection potentiated by silica exposure include increased ease of establishing infection, higher tissue counts of viable organisms, and increased lethality.[6] The effects of silica on *M tuberculosis* infection are attributed to its direct inhibitory ac-

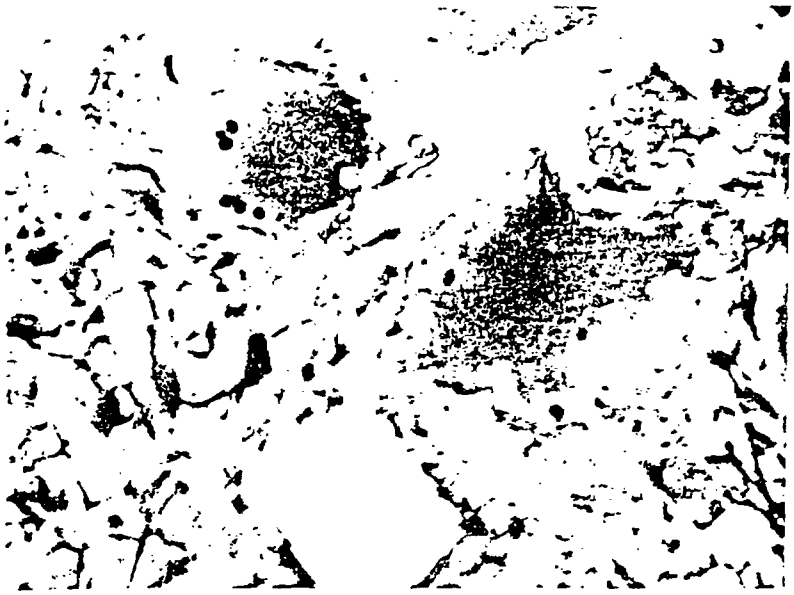

Fig 2.—Bone marrow giant cells with intracellular yeasts (Grocott's methenamine silver stain, ×280).

Fig 3.—Electron-microscopic examination revealing needle-shaped crystals (arrows) in lymph node macrophages (×22 500).

xic effects on mononuclear phago-tes.[8] At sublethal doses, silica mark-lly increases the multiplication of *M berculosis* in long-term peritoneal crophage cultures in a dose-depen-ent manner.[8] Potentiation of myco-acterial growth in vivo is also dose-ependent. Humans exposed to silica ust have a much higher incidence of berculosis than nonsilicotic persons om similar geographic locales.[8] In ct, prior to the availability of anti-ycobacterial chemotherapy, tuber-losis was the major cause of death classic silicosis.[8] Additionally, sili-tic humans have a less favorable sponse to antimycobacterial chemo-erapy than nonsilicotic humans.[8] A cent article described an intrave-us drug abuser with disseminated c granulomatosis and miliary erculosis.[3] The authors proposed at the substantial phagocytosis of c crystals by macrophages facili-ed the spread of *M tuberculosis*.

Immune lymphocytes from *H cap-ulatum*-infected mice must activate crophages in order for the phago-es to kill endocytosed fungi.[8] This ration is at least partially attrib-d to soluble factors, perhaps uding interferon gamma, released immune T-lymphocytes.[8] In sys-temic histoplasmosis, mononuclear phagocytes of the reticuloendothelial system cannot kill engulfed fungi.[1] It is unclear whether the lack of intracellular killing is due to an intrinsically inadequate macrophage digestive mechanism or to a failure of lymphocytes to activate macrophages. Regardless of mechanism, decreased killing of yeasts by macrophages increases the likelihood of systemic disease following infection with *H capsulatum*. Inbred or random-bred mice inoculated intravenously with silica 1, 14, or 21 days before exposure to *H capsulatum* showed greater susceptibility to infection than mice not treated with silica.[10] Manifestations of increased susceptibility included an increase in the number of viable organisms recovered from spleens of killed mice, lower body weights, and increased mortality. Intravenous silica administration also decreased the blastogenic response of mouse splenocytes to T-cell mitogens (ie, Con A and phytohemagglutinin [PHA]), but not to be a B-cell mitogen (ie, lipopolysaccharide).[10] The blastogenic response of T-cells to PHA and Con A is macrophage-dependent, whereas, the response of B-cells to lipopolysaccharide is macrophage-independent. This, in conjunction with the in vitro finding that silica particles were toxic to macrophages but not lymphocytes, indicated that silica inhibited T-cell blastogenesis indirectly via depressing macrophage functions.[10] Thus, silica increased the severity of histoplasmosis in infected mice by: (1) inhibiting macrophages effector mechanisms (ie, phagocytosis and intracellular killing); and (2) inhibiting macrophage-dependent immune functions (ie, T-cell blastogenesis leading to macrophage activation).

We have described the case of an intravenous drug abuser with systemic talc granulomatosis and disseminated histoplasmosis. He was not iatrogenically immunosuppressed, he did not have a hematologic malignancy, and he was not predisposed to disseminated histoplasmosis by age. Although he was at high risk for developing acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC), immunologic studies were not consistent with this diagnosis. The T_{helper} (T_4): $T_{suppressor}$ (T_8) ratio was slightly depressed (0.62) due to an elevated number of T_4-cells; total T and T_8 cell numbers were normal. This finding is consistent with disseminated histoplasmosis.[11] In AIDS and ARC, the aberrant T_4:T_8 ratio is usually due to a decrease in the number of T_8 cells.[12] The patient also had a moderately depressed T-cell blastogenic response to PHA and Con A. The

decrease was probably due to systemic fungal infection, or perhaps, disseminated talc granulomatosis.[10] Additional indications that the patient did not have AIDS or ARC were a markedly positive histoplasmin skin test, recovery from histoplasmosis with amphotericin B therapy, and subsequent survival for over three years. Hé has been seen as an outpatient on several occasions over the three years and showed no physical signs of AIDS, ARC, or opportunistic infections. Thus, although the patient was not tested for antibody to HIV, it is clear that he was not predisposed to disseminated histoplasmosis by HIV infection.[2,12] Phagocytosis and intracellular killing of yeasts by mononuclear phagocytes of the reticuloendothelial system are crucial to an uneventful, self-limited illness following *H capsulatum* infection.[1] Silica, which is closely related to talc, is directly toxic to macrophages; inhalation or intravenous exposure to silica lowers resistance to histoplasmosis, tuberculosis, and other infectious diseases in which macrophage function is crucial.[4] We propose that the patient lowered his macrophage-mediated resistance to *H capsulatum* infection by repeated intravenous talc administration.

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Cystic Hypersecretory Duct Carcinoma of the Breast

Report of a Case With Fine-Needle Aspiration

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• A patient with a recently described rare histologic variant of ductal carcinoma of the breast, so-called cystic hypersecretory duct carcinoma, is described. The findings on fine-needle aspiration biopsy, and to our knowledge, the first cytologic study of this entity reported in the literature, are described and differentiated from mucinous carcinoma and benign mucocelelike lesions. The histologic differential diagnosis, with an emphasis on benign lesions that may have a predominant cystic component, is also discussed.

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Cystic hypersecetory duct carcinoma (CHDC) of the breast, a rare histologic variant of intraductal carcinoma recently described by Rosen,[1] is characterized by the formation of variably sized cysts that contain an eosinophilic secretory product reminiscent of thyroid colloid, and by micropapillary carcinoma occurring both within some, but not all, of these cysts, as well as in adjacent nondistended ducts. We describe a patient with CHDC, who had initially undergone biopsy and was diagnosed as having benign fibrocystic disease in 1981. Five years later, in 1986, the lesion recurred locally and was evaluated by fine-needle aspiration (FNA). A subsequent incisional biopsy specimen confirmed the diagnosis of CHDC and the patient underwent modified radical mastectomy. To our knowledge, this is the first description of FNA cytologic features of CHDC and its distinction from both mucinous (colloid) carcinoma and benign mucocelelike lesions. In addition, the histologic differential diagnosis of CHDC will be discussed, particularly since its deceptively bland low-power appearance can be confused with a variety of benign breast diseases.

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