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Mycosis Fungoides with Thrombotic Microangiopathy and Major Central Nervous System Manifestations

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A case of mycosis fungoides is presented which terminated in death by an acute central nervous system illness. Autopsy revealed thrombotic microangiopathy. This is felt to be the first report of thrombotic thrombocytopenic purpura occurring in a patient with mycosis fungoides. Since thrombotic thrombocytopenic purpura has been reported in association with other malignancies, the association of these relatively rare disorders may represent more than a coincidence.

Mycosis fungoides (MF) is a malignant reticulosis arising within the skin. Its position in the lymphomatous disorders is controversial, although many authors accept it as a distinct disease entity on clinical and histological grounds. Visceral involvement is common and can be the immediate cause of death.

A variety of central nervous system effects of mycosis fungoides have been reported and will be reviewed here. The present case of mycosis fungoides was terminated by an acute central nervous system illness found, at autopsy, to be a thrombotic microangiopathy. Although the latter disorder has been found in association with other malignancies, the present combination of diseases to our knowledge has never been previously published.

Case Report

This 58-year-old, Negro female was first seen in the Henry Ford Hospital Dermatology Clinic in January of 1968 when she presented with a generalized eruption. She gave the history of having developed hives after eating tomatoes. A provisional diagnosis of skin allergy was made with the possibility of mycosis fungoides. There was no follow-up because she left for Tennessee.

The patient was next seen in the Emergency Room of the Hospital on August 6, 1968, with epigastric pain, nausea, vomiting, bilateral supraorbital headaches, and lethargy. There had been a 10-pound weight loss over a two-month period. She had a previous history of hypertension.

On physical examination, the patient was in moderate distress and had a generalized pruritic eruption. There were numerous areas of hypopigmentation with other areas of hyperpigmentation; numerous plaques and papules showed changes of lichenification and several showed excoriations. All of the lesions, which covered the entire body including the palms and soles of the feet, were covered by a fine scale. The remainder of the physical examination was unremarkable except for minimal arteriovenous compression seen in the fundus, a grade II/VI systolic ejection murmur at the right apex, and blood pressure of 210/
There were no abdominal masses. Neurologic examination was negative except for lethargy.

**Laboratory Data**

Hemoglobin was 8 grams per cent, white count 22,200 with a distribution of 70% polymorphs, 23% lymphocytes and 3 atypical lymphs; platelet count was 26,900 cu mm. Tests of liver function were normal. BUN was 32, blood sugar 66 mg %, VDRL was nonreactive and urine porphobilinogen negative. Urine: specific gravity 1.006, 4 plus albumin, numerous white cells with a few coarse granular casts and 4 to 5 red blood cells per high powered field. Blood cultures taken during this patient’s febrile illness were negative. A lupus erythematosus preparation was negative as were barbiturate and salicylate levels. Spinal fluid was unremarkable. Complement fixation for cytomegalic inclusion virus was less than 1:4. The bone marrow showed increased cellularity with a ME ratio of 2.5:1.0. Normoblasts and megakaryocytes were increased. No tumor cells or granulomata were found. Following admission, an excisional biopsy performed on one of the skin lesions of the left forearm disclosed the plaque stage of mycosis fungoides (Fig 1).

**Hospital Course**

The patient underwent a stormy febrile course, with increasingly impaired cerebration. Skull x-rays and echograms of the skull were normal except for the possible postglenoid thinning. The brain scan was class III with increased activity on the right anterior side. For this reason a right carotid arteriogram was carried out and was normal. A lumbar puncture was also normal. The impression of the neurologist was that metabolic and/or toxic factors were probably responsible for her central nervous system manifestation.

Starting August 8th, the patient devel-

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**Figure 1**

Skin biopsy shows heavy pleomorphic lymphohistiocytic infiltrate within the dermis. Note Pautrier’s microabscess and abnormal reticulum cells. X 390 H & E reduced 22%
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oped numerous clonic convulsions. Anti­convulsant therapy failed to alleviate this condition and the patient expired on August 11, 1968.

Autopsy Data

The patient was a well-developed, well-nourished Negro female of 133 pounds. The skin over the entire body showed numerous small and large plaques some of which were hyperpigmented, others hypopigmented and several excoriated. These ranged in size from 0.5 up to 1.0 cm.

Abnormal findings in the viscera were as follows: The heart weighed 425 grams and appeared to have left ventricular enlargement. Examination of the valve cusps revealed numerous small rather firm vegetations on the superior surfaces of mitral and aortic valves (Fig 2). These vegetations measured, on an average, 0.2 cm in diameter. Throughout the myocardium, several small petechial hemorrhages and areas of yellowish discoloration and necrosis were noted.

The visceral pleura revealed numerous petechiae especially over the lower lobes which were firm in consistency. The liver had multiple small hemangiomata on cross section, the largest of these was 1.8 cm in diameter. The spleen was normal in size and appearance. Gastrointestinal tract, pancreas, genitourinary organs, vascular system and the skeletal system were unremarkable.

The brain weighed 1250 grams and showed generalized edema with multiple small petechial hemorrhages in the left upper parietal cortex. The larger cerebral vessels were unremarkable.

Microscopic Pathology

On sections of a few random skin lesions, the dermis was composed of an avascular layer of thick hyalinized connective tissue with almost complete loss of dermal appendages. The epidermis showed moderate

Figure 2

Large friable mitral valve vegetations.
hyperkeratosis and parakeratosis with some flattening of the rete pegs. These sections were more representative of the late stages of poikiloderma atrophicans vasculare and did not resemble the appearance of mycoses seen in earlier surgical biopsy.

The most important findings in the viscera were the presence of multiple platelet thrombi involving the systemic arterioles and capillaries. These thrombi were most marked in the heart, kidneys, and the brain, although lungs, liver, spleen, pancreas, and adrenals all showed vascular thrombi to some extent.

In the myocardium the thrombi were very extensive and involved most of the capillaries (Fig 3). The capillary walls showed varying degree of endothelial reaction. An occasional area of myocardial necrosis with polymorphonuclear reaction was found but large infarcts were not noted. The endocardial vegetations were composed of platelets and fibrin only, without bacterial growth.

The underlying endocardium was edematous. In the brain the arterioles and capillaries of the basal ganglia and the left parietal cortex were especially involved by the thrombi (Fig 4). Perivascular edema and a small parietal lobe infarct were concomitant findings. Sufficient lesions were found within the basal ganglia, brain stem and cerebrum to explain the convulsions which the patient had exhibited.

None of the sections of the viscera showed infiltrates corresponding to mycoses fungoides.

Discussion

Visceral involvement is common in MF but reports vary greatly as to the frequency of dissemination to internal organs. Bluefarb found visceral metastasis to be rare, while Gall reported an

Figure 3

Marked endothelial hyperplasia around fibrin-platelet thrombi. Inflammatory reaction is virtually nonexistent. X 390 H & E reduced 20%
incidence of 46\%; Cawley et al\textsuperscript{4} found an incidence of 80\% and Block et al\textsuperscript{1} 82\%. The nature of the metastatic infiltrates varied—some were similar to that of the primary cutaneous process, while others were indistinguishable from more malignant lymphomatous diseases.

The lymph nodes, bone marrow and spleen are the organs most commonly involved in disseminated MF and almost every organ has exhibited histologic evidence of invasion; however, metastasis to the central nervous system is rare, even in cases with generalized involvement. Although several such cases are included in reviews of disseminated MF,\textsuperscript{1, 5, 6} the authors do not describe the nature and extent of the nervous system findings. Riecke,\textsuperscript{7} Kobner,\textsuperscript{8} Cawley et al\textsuperscript{4} reported cases of MF with metastatic involvement of the dura mater, but no symptoms referable to the nervous system. Pautrier's case\textsuperscript{9} had involvement of the dura and pia mater and Hemmingson's patient,\textsuperscript{10} also asymptomatic, had choroid plexus involvement.

Breakley, one of the first to report central nervous system involvement in
a patient with MF, found an infiltrate in the gray and white matter of the cerebral hemispheres.\textsuperscript{11} A patient described by Paltaut et al\textsuperscript{12} had involvement of the right oculomotor, trigeminal and femoral nerves, sparing the brain substance. Moncorps et al\textsuperscript{13} reported the case of a 35-year-old male who developed abnormalities of most cranial nerves, and increased intracranial pressure several months after the appearance of cutaneous MF. Necropsy revealed a cellular infiltrate similar to that of the skin about all cranial nerves, the pia mater, corpora quadrigemina and left caudate nucleus.

Brandweiner\textsuperscript{14} reported the case of a 50-year-old male who had cutaneous lesions of MF for 30 years. He then developed rightsided hemiplegia and rightsided deviation of the head and eyes. Needle prick sensation was normal and Babinsky’s sign negative. At autopsy, “hazelnut” to “apple” size nodules seen within the brain substance were felt to represent metastasis along vessels from the cutaneous process.

The famous physiologist, W. B. Cannon\textsuperscript{15} had a 14-year history of MF. He experienced a loss of taste for sweets on the right side of the tongue, together with a rightsided facial paralysis and bilateral deafness. Because the symptoms responded to irradiation, they were felt to represent neural invasion. Postmortem examination confirmed visceral dissemination of the disease but no mention was made of central nervous system findings.

Rosai and Spiro\textsuperscript{16} presented an interesting case of a 79-year-old female with a one-year history of MF. She developed a seventh nerve palsy, leftsided weakness and increasing lethargy, but no papilledema and meningismus. Necropsy showed multiple foci of demyelinization in the brain and cerebellum and a polymorphous perivascular inflammatory reaction with numerous atypical histiocytes throughout the brain. The infiltrate was similar to that of the skin lesions. A 1967 CPC from Barnes Hospital describes a case of MF in which major neurologic manifestation proved to be due to invasion of the central nervous system by tumor along with focal demyelination. MF and neuromyopathy were reported by Kurwa and Payne,\textsuperscript{18} similar to the association of neuromyopathy with carcinoma and lymphoma observed by Brain et al.\textsuperscript{19} The patient, a 67-year-old male, experienced difficulty ascending stairs and rising from a chair almost simultaneously with the development of cutaneous MF. The process rapidly progressed, leaving the patient almost bedridden. Shortly before hospitalization he awoke with complete paralysis of the left hand. Examination revealed weakness and wasting of the hand, arm, and leg muscles with fasciculation of the thigh muscles. Autopsy showed small foci of degeneration of the white matter with some loss of anterior horn cells along the spinal cord and mild degeneration in the pyramidal tracts. No tumor was noted in the central nervous system or viscera.

MF is not frequently associated with other disease states. Bluefarb\textsuperscript{2} culled from the literature case reports of MF occurring with carcinoma, lupus erythematosus, Addison’s disease, Kaposi’s sarcoma, leukemia and deep mycoses. He did not feel that MF progressed to other lymphomas. However, many authors believe that a mutability exists among the lymphomatous diseases. Patients with histologically con-
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firmed MF were reported to undergo transition to Hodgkin's disease, lymphosarcoma or reticular cell sarcoma in 34% of the cases collected by Cyr et al and 16% by Block et al. The cardinal features of thrombotic thrombocytopenic purpura form a pentad consisting of thrombocytopenic purpura, hemolytic anemia, fever, neurologic manifestations and renal disease. Diagnosis is confirmed by histologic evidence of widespread hyaline occlusion of terminal arterioles and capillaries. None of these findings are common in patients with mycosis fungoides and there is general agreement that MF lacks pathognomonic hematologic findings. Anemia, which is not infrequent, is never hemolytic in origin, and platelet counts in MF are generally normal.

Capillary thrombosis has been observed in patients with malignant tumors as well as those with acute or chronic leukemia, but it has not been reported previously in patients with MF. Thrombotic thrombocytopenic purpura (TTP) has been reported to be associated with systemic lupus erythematosus, polyarteritis nodosa, malignant nephrosclerosis and rheumatism. A few cases were associated with malignant tumors, ie, acute myeloid leukemia and malignant thymoma. A Japanese study reported on observations of TTP in a patient with acute myelocytic leukemia, and in two patients with gastric carcinoma. The TTP was the direct cause of death. These authors, using the fluorescent antibody method, concluded that the thrombi of arterioles and capillaries in these cases were composed of platelets and fibrin or fibrinogen.

The thrombotic phenomena which occur in large veins in association with certain cancers, especially cancer of the pancreas, is well known. Although the incidence of malignant disease with microangiopathy is sufficiently rare that the possibility of coincidence is strong, this case brings the total number of reported cases only to six. It is interesting that many observers regard TTP to be an immunohematologic or autoimmune disorder which belongs to the spectrum of collagen disease like lupus erythematosus and dermatomyositis. The collagen diseases in turn have a fairly high incidence of coexistent neoplasm. Komori states that any pathogenic relationship between primary malignant disease and TTP resembles acquired hemolytic anemia in which idiopathic and symptomatic forms occur.

Summary

A case is reported of mycosis fungoides with rapid death due to thrombotic thrombocytopenic purpura. The association of these two relatively rare disorders is reviewed.

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