OCULAR MANIFESTATIONS OF SARCOIDOSIS

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OCULAR lesions occur in approximately 50 per cent of patients having sarcoidosis. It is the purpose of this paper to review these manifestations, to discuss their possible diagnostic significance and their treatment, and to summarize the findings in 11 patients.

Sarcoidosis is a ubiquitous disease of unknown etiology. Although it has received much attention in the literature of the past 50 years, no specific therapeutic agent has yet been found. In 1948 the Committee on Sarcoidosis of the National Research Council of the United States[1] defined sarcoidosis as:

> . . . a disease of unknown etiology. Pathologically it is characterized by the presence in any organ or tissue of epithelioid cell tubercles with inconspicuous or no necrosis and by the frequent presence of refractile or apparently calcified bodies in the giant cells of the tubercles. The lesions may be replaced by fibrosis, hyalinization or both. Clinically, the lesions may be widely disseminated. The tissues most frequently involved are the lymph nodes, lungs, skin, eyes, and bones (particularly of the extremities). The clinical course usually is chronic with minimal or no constitutional symptoms. However, there may be acute phases characterized by malaise or fever. There may be signs or symptoms referable to the tissues and organs involved. The intracutaneous tuberculin test is frequently negative. The plasma globulins are often increased. The outcome may be clinical recovery without radiographically visible residue or there may be impairment of the organs involved, or a continued chronic course of the disease.

Sarcoidosis affects young adults of both sexes. Most reports indicate that Negroes are more susceptible than white people, in ratios up to 16:1.[2] It has been observed in persons in all parts of the country; however, Michael, Cole, Beeson, and Olson[3] found in a follow-up of 226 patients (both white and Negro), originally reported by Ricker and Clark,[4] that most of the patients had come from the southeastern section of the United States.

A characteristic feature of sarcoidosis is the lack of direct correlation between the severity of symptoms and the extent of involvement. The general health of the patient often is good, although he may lose some weight and have febrile periods. Almost any part of the body may be affected. The lungs most frequently are involved and roentgenograms show a reticular infiltration that is most pronounced near the hili, and an increased hilar shadow resulting from hilar lymphadenopathy. There may be enlargement of other lymph nodes throughout

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the body. Involvement of the bones, usually the phalanges, results in punched-out cystlike areas or in a lattice-like diffused involvement. Disseminated nodules may appear in the skin—most often in that of face, forearms, neck, shoulders, and legs. Similar nodules may occur in nerves, pleura, pericardium, prostate, skeletal muscles, spleen, liver, and kidneys.

Laboratory studies frequently show a reversal of the albumin-globulin ratio in the blood plasma. There sometimes are an increased sedimentation rate, a slight rise in blood calcium, and a mild eosinophilia. Some patients have false-positive blood Wassermann reactions. Most patients have anergy to tuberculin; whether this is an actual entity or is only a factor of epidemiology was questioned by Michael and associates.[3] Of the 226 patients mentioned previously, most came from rural areas where one would expect a greater percentage of the population to show anergy to tuberculin.

The most recent and helpful aid in the diagnosis of sarcoidosis is the Kveim test,[5,6] in which the patient receives an intracutaneous injection of specially prepared macerated sarcoid lymph node. In patients with active sarcoidosis the injection causes the formation of a fresh sarcoid nodule which is biopsied and examined histologically about six weeks after injection. The Kveim test also may be used to determine the progress of the disease: when the disease is in remission, the test is negative.

Ocular Manifestations

Sarcoidosis may affect almost any portion of the eye, but the uveal tract is most frequently involved. Woods[7] reported that the eyes were involved in 44 per cent of 94 patients. Longcope[8] found ocular involvement in 16 of 31 patients (23 of whom were Negroes); in 12 of the 16, the ocular involvement was the first manifestation of the disease. The uveal tract was involved in 13 patients, the cornea in 5, the conjunctiva in 2, and in 1 patient each, the sclera, the retina, the choroid, and the optic nerve. Uveoparotid fever also was present in 7 of the 16 patients. In a review of 100 patients with sarcoidosis reported by other authors, Levitt[9] noted that 43 patients had ocular lesions. In this group the uveal tract was involved in 28 patients of whom 10 had phthisis bulbi, the lacrimal glands in 9, the lids in 7, and the conjunctiva in 6.

The following is a description of the manifestations of sarcoidosis in the eye and its adnexa.

Uveal tract. Inflammation of the anterior uveal tract is the most frequent ocular manifestation of sarcoidosis. There is no relationship between the onset of the ocular inflammation and that of any other manifestation of the disease. The iritis usually is painless, inflammatory symptoms are slight, and synechia is common. The typical clinical picture is that of a nodular type of iritis. The nodules usually are superficial, but may lie deep in the stroma. The nodules of sarcoid are said to be larger, more pink, more irregular, and more vascular than true miliary tubercles. It is questionable that the type of vascularization of the nodule in sarcoidosis is pathognomonic, as it differs little from that of the tubercle in tuberculosis. However, in sarcoidosis the vessels form an interlacing pattern in and over the nodule, whereas in tuberculosis the vessels pass over and

around the tubercle and invade the surrounding iris.[7] The large keratic precipitates of the "mutton-fat" type also are typical of sarcoidosis. On occasion there may be considerable inflammation with the development of a heavy plastic iritis. If the parotid gland becomes swollen, Heerfordt's disease (uveoparotid fever) develops. There also may be cranial nerve palsies, especially of the facial nerve. Walsh[10] has observed transient palsies of all the cranial nerves except the eleventh and twelfth.

Lacrimal glands. Sarcoidosis may produce a painless swelling of one or both lacrimal glands. The enlarged gland is not attached to the skin and is of firm, somewhat nodular consistency. Often there is an associated involvement of the submaxillary and salivary glands and of cervical lymph nodes producing Mikulicz's disease.

Conjunctiva. Lesions of the conjunctiva are comparatively rare. Small nodules or large follicles may occur in the palpebral conjunctiva, bulbar conjunctiva, or cul-de-sac. The lesions are grey, yellow-brown, or yellow-red, and are firm, painless, and movable.

Lids. On the lids cutaneous lesions may occur which exactly duplicate those on other parts of the body. Small, painless, firm, subcutaneous nodules that histologically are typical of sarcoid also may occur. These lesions may be the only manifestation of the disease or they may be associated with other lesions.

Cornea. It is doubtful that sarcoid nodules ever occur primarily in the cornea; corneal lesions usually are in association with uveitis. In such cases the lower part of the cornea is most frequently involved with a descemetitis and an interstitial keratitis.

Sclera. Although involvement of the sclera has been reported, Woods[7] states that there is no evidence of true scleral involvement in any of the reported cases.

Fundi. Sarcoid lesions of the fundi are comparatively rare. Yellowish nodules of the choroid have been observed. Walsh[10] observed in a patient a choroidal mass of 8 diopters in the left eye, bilateral optic atrophy, and small retinal masses. Periphlebitis may accompany the retinal lesions.

Findings in 11 Cases

Our findings in 11 patients having ocular manifestations of sarcoidosis are summarized in the table. The ages ranged from 21 to 70 years, but seven patients were from 21 to 32 years of age. Six of the patients were women, and five were men. Three of the patients were Negroes (two women and one man).

Laboratory findings. Most of the laboratory results were typical of sarcoidosis. Anergy to tuberculin was demonstrated in eight of the nine patients tested; the result in one patient was not recorded. The Kveim test was positive for sarcoidosis in six of the nine patients tested; the result was negative in two; it was not recorded for one patient. In one of the patients whose test was negative the sarcoidosis was thought to be in a state of remission; in the other patient it was found that a weak, equivocal antigen had been used. Abnormalities, consisting most frequently of a hilar adenopathy, were present on the roentgenograms of the chest of 10 of the 11 patients. There was a reversal of the albumin-globulin ratio in four of six patients tested. The blood eosinophil counts for five patients were: 0, 2, 3, 4, and 6 per cent, respectively. The sedimentation rate studied in five patients was increased in two, equivocally increased in two, and normal in one. The blood Wassermann test was negative in all 11 patients.

Ophthalmologic findings. As in all other published reports the uveal tract was the portion of the eye most frequently affected. Ten of the patients had

Table. — *Data for 11 patients having sarcoidosis*

Patient no.	Patient's			Laboratory findings							Ocular manifestations	Treatment	
	Sex	Race	Age, yr.	Tuberculin	Kveim test	Albumin: globulin ratio	Eosinophil, %	Sedimentation rate	Serology	Roentgen findings in chest		Local	Systemic
1	F	W	29	–					Negative	+	Heerfordt's disease (uveoparotid fever), superficial keratitis, cysts of the iris	Atropine and merthiolate ointment	None
2	M	W	29	–		Normal	4	Increased(?)	Negative	+	Iritis	Unknown	Irradiation to chest
3	F	W	24	–	+				Negative	+	Heerfordt's disease (uveoparotid fever), superficial keratitis	Atropine	Calciferol
4	M	W	42	–	+		2	Increased	Negative	+	Heerfordt's disease (uveoparotid fever)	Atropine	Calciferol
5	F	W	53	–	–	Reversed	6		Negative	+	Iritis	Cortisone and atropine	Nitrogen mustard
6	F	W	43	–	?	Normal			Negative	+	Iritis	Cortisone and atropine	Cortisone orally
7	F	N	25	?	+	Reversed		Normal	Negative	+	Iritis, secondary glaucoma	Cortisone and atropine; paracentesis	Cortisone and ACTH, followed by isoniazid
8	M	N	27	–	+	Reversed	3	Increased	Negative	+	Iritis	Cortisone and atropine	Isoniazid followed by cortisone
9	F	N	32		+				Negative	+	Papules on lids, inactive iritis, old descemetitis, keratitis	Zinc and Adrenalin drops	Isoniazid
10	M	W	21	–	+	Reversed	0	Increased	Negative	+	Right eye: old chorioretinitis. Left eye: large mass covering disc	None	Cortisone, ACTH, isoniazid
11	M	W	70		–				Negative	–	Iritis	Cortisone and atropine	Isoniazid

evidence of an anterior uveitis that was active; three of these also had Heerfordt's disease (uveoparotid fever).

Treatment and results. The patients were treated during the past seven years, and accordingly the changes in treatment reflect the therapeutic progress of the period. In the table the cases are listed in chronologic order according to the date of initial examination. The patient seen earliest (Patient 1) received no medication for her systemic disease. Atropine and merthiolate ointment were recommended for topical treatment of her eyes, but she was examined only once, and the results of treatment are unknown. Two of the other early patients received calciferol. It is not known what treatment, if any, Patient 2 received for iritis. The only known systemic therapy was irradiation to his chest administered in another hospital to prevent the development of Hodgkin's disease. For Patient 3 atropine alone, topically applied to the eyes, gave excellent improvement in the severe iritis. (This patient was one of identical twins, both of whom had sarcoidosis but the other twin had no ocular manifestations. The case was reported by Rogers and Netherton.[11]) In Patient 4 it was recommended that the pupils be kept dilated with atropine, but the results are not known.

In five patients (5, 6, 7, 8, and 11), most recently seen, iritis was treated by topical application of cortisone and atropine. In each, the iritis subsided although there was mild recurrence in some patients. Patient 5 obtained a remission of her generalized disease after a course of nitrogen mustard therapy. Patient 6 received cortisone orally and since then has had no systemic manifestations of the disease. Patient 7 received a short course of cortisone orally and corticotropin (ACTH) intramuscularly, followed by a longer period of isoniazid therapy orally; her condition also improved. For Patient 8 the administration of isoniazid was stopped after two months when he developed iritis; the oral administration of cortisone and the local application of cortisone and atropine were begun and the patient became symptom-free. Patient 11 now is receiving only isoniazid systemically, and the skin lesions are disappearing.

The condition of Patient 10 who has the large mass involving the optic disc has not yet shown any improvement. He received cortisone, ACTH, and isoniazid systemically. It would seem that the extent of involvement is too great to hope for any appreciable restoration of function of the optic nerve.

Discussion

Patients having iritis who demonstrate anergy to tuberculin, possibly may have sarcoidosis; however, if the iritis is definitely granulomatous, the possibility of the presence of sarcoidosis is even greater. In such cases a Kveim test should be performed in addition to study of the plasma proteins and routine diagnostic measures such as roentgen study of the chest and differential blood count. A biopsy of lymph nodes also occasionally may be advisable. Some form of therapy should be started before the results of the Kveim test are known, since the test requires six weeks.

At present, there is no specific therapeutic agent for sarcoidosis. Many types

of therapy have been used, including administration of chaulmoogra oil, sulfones, antibiotics, vitamins, nitrogen mustard, calciferol, dihydrotachysterol, phototherapy, and irradiation. These measures have been replaced by the administration of isoniazid and cortisone, which seem at the present time to offer the best form of treatment. However, Patient 8 developed iritis after taking isoniazid for two months for systemic sarcoidosis. Increased tendency to bleed also has been reported as occurring in some patients being treated with isoniazid.[12,13] Wacker and Bonard[12] noted an increased coagulation time in one third of the patients and clinical manifestations of increased tendency to bleed in some of the patients receiving isoniazid. Schlaegel and Hungerford[13] believe that isoniazid may have aggravated the hemorrhagic tendency of some of the fundal lesions in their patients. One of our patients without ocular manifestations of sarcoidosis (not included in this series), after four weeks of treatment with isoniazid, developed retinal hemorrhages as a part of isoniazid intoxication. Certainly one patient represents a very small percentage of the number of patients who have been treated here with isoniazid during the past few years. The possibility exists, however, that other patients may have had hemorrhages that went undetected because they were too small or too few to cause visual disturbances, and therefore funduscopic examinations with mydriasis were not performed.

Schlaegel and Hungerford[13] administered isoniazid to one patient having tuberculous uveitis. Although there was a definite but delayed improvement in the patient's condition, the authors proposed that the favorable response might have been a coincident spontaneous improvement.

The iritis caused by sarcoidosis probably is best treated by local applications of cortisone and atropine. This treatment resulted in remission of the iritis in all five patients to whom it was administered in this series (Patients 5, 6, 7, 8, and 11). Dahlene[14] reported that local application of these drugs in combination with oral administration of cortisone resulted in dramatic improvement in vision of one patient having sarcoidosis with iritis. Ozazewski and Bennett[15] compared the results of treatment in three patients having sarcoidosis. No improvement in vision occurred in one patient who received a total of 360 mg. of corticotropin, or in another patient who received a course of old tuberculin followed by a total of 100 mg. of urethan. However, there was pronounced improvement in vision of the third patient who received a total of 240 mg. of corticotropin systemically and cortisone locally: vision improved from nil to 20/70 in the right eye and from light perception to 20/30 in the left eye.

Some mild exacerbations of the iritis have occurred in our patients and in those reported by others who were treated with cortisone and atropine, but "rebound phenomenon" never has occurred. Rebound phenomenon—severe exacerbation when cortisone therapy is stopped—has been observed in patients having tuberculous ocular disease.[16]

Summary

Approximately 50 per cent of the cases of sarcoidosis are associated with

ocular manifestations, most of which occur in the uveal tract. Of 11 patients having sarcoidosis, 10 had involvement of the uveal tract (inactive in only 1), 3 of whom had Heerfordt's disease (uveoparotid fever). Three patients also had corneal involvement secondary to the uveitis, and one patient had typical skin lesions on the eyelids. The one patient not having manifestations in the uveal tract had extensive involvement of the optic disc in one eye and of the choroid and the retina in the other.

The topical application of cortisone and atropine to the eye seems at the present time to be the most effective treatment of anterior uveitis resulting from sarcoidosis. However, the patients also should receive treatment for the systemic manifestations of the disease.

In a patient having a granulomatous type of uveitis who demonstrates anergy to tuberculin, sarcoidosis may be present. It is recommended that in such a patient special diagnostic tests, particularly the Kveim test, be performed in addition to the routine diagnostic measures.

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