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EDITORIAL

Sarcoid Uveitis

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Sarcoidosis is a multi-system chronic inflammatory disorder of unknown etiology characterized by the formation of non-caseating granulomas in involved tissues. Although sarcoidosis may affect individuals of any race and age, it occurs most frequently during the third through fifth decades of life. Scandinavians and African Americans are at three to four fold increased risk of developing the disorder, and the lung and/or thoracic lymph nodes are involved in over 90% of patients.[1,2] The prevalence of ocular involvement observed in clinic-based cohorts has varied widely, from less than 10% in Finland to over 70% in Japan.[3,4] Baughman et al. studied 736 patients with biopsy-proven sarcoidosis seen within 10 months from diagnosis at 10 referral centers in the United States and identified eye involvement in 11.8% of patients.[5]

While a wide range of ocular manifestations of sarcoidosis have been reported, uveitis appears to be most common, with over 80% of patients with sarcoid uveitis having bilateral disease.[6–16] Definitive diagnosis of ocular sarcoidosis requires characteristic biopsy findings along with exclusion of other possible causes of ocular inflammation, particularly tuberculosis.[17,18] An International Workshop on Ocular Sarcoidosis (IWOS) met in Tokyo in October, 2006, and through consensus proposed that patients with compatible uveitis and bilateral hilar adenopathy, but no biopsy, be considered presumed ocular sarcoidosis; those with neither a biopsy nor hilar adenopathy, but at least three suggestive intraocular signs and two supportive investigational tests, be considered probable ocular sarcoidosis; and those with a negative biopsy, but at least four suggestive intraocular signs and two supportive studies be classified as possible ocular sarcoidosis. Suggestive ocular signs included mutton-fat keratic precipitates (both large and small) and/or iris nodules; trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae; snowball vitreous opacities; peripheral chorioretinal lesions/scars; nodular and/or segmental periphlebitis and/or retinal macroaneurysms; optic disc nodules/granulomas and/or solitary choroidal nodules; and bilaterality. Supportive studies included a negative tuberculin skin test in a patient known to have had either BCG vaccination or a prior positive PPD skin test; an elevated serum angiotensin-converting enzyme (ACE) or lysozyme level; bilateral hilar adenopathy on chest x-ray or chest CT; and abnormal liver enzymes (any two of alkaline phosphatase, AST, ALT, LDH, or γ-GT). Two original articles[19,20] and two letters to the editor[21,22] in this issue of *Ocular Immunology & Inflammation (OII)* present important findings relevant to the clinical presentation, progression, and pathogenesis of sarcoid uveitis.

Nagata et al. study a cohort of 84 patients with sarcoid uveitis seen at two uveitis referral centers in Japan.[19] The diagnosis was confirmed by tissue biopsy in all patients, including 54 with positive lung (64.3%) and 30 with positive skin (35.7%) biopsy. Sixty-two (73.8%) were female and 22 (26.2%) were male. Patients were stratified by age and defined as younger if they were equal to or less than 45 years of age. Using this definition, 57 patients (67.9%) were defined as older, whereas 27 (32.1%) were younger.

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The proportion of men was identical in the younger versus older age groups (11/22 = 50%), whereas older patients overall tended to be female (46/57 = 80.7% versus 16/27 = 59.3%; nominal p value = 0.04; two-tail uncorrected Chi square test). The uveitis was bilateral in 72 patients (85.7%). The authors divided the fundus into three Zones (I, II, III), similar, although not identical, to Zones 1, 2, and 3 introduced to study viral retinitis in patients with HIV/AIDS.[23] Unfortunately, the anterior limit of Zone I was not defined in relation to either the optic disc or arcade vessels, and the precise nature of the posterior segment lesions was not described. The inflammation involved the anterior, intermediate, and posterior segments (i.e. panuveitis) in 74 patients (88.1%). Only three (3.6%) patients had inflammation limited to the anterior segment with no posterior segment involvement and all three were in the younger cohort. Of the 24 younger patients with lesions involving the posterior segment, only 10 (41.7%) had Zone I lesions. Chi-square testing of posterior segment lesion location by patient age suggested that Zone III lesions were more common in the older group (78.9% versus 58.3%; p value = 0.04) and that Zone I lesions tended to be more common in younger patients (41.7% versus 19.3%; p value = 0.09). These p values were not corrected for multiple testing, however, and so should be considered to be nominal. The authors found no correlation between posterior segment lesion location and gender. These data suggested that biopsy-proven ocular sarcoidosis in tertiary referral centers in Japan was predominantly a disorder of women at or beyond the fifth decade of life, and was typically both bilateral and diffuse in that it involves the anterior, intermediate, and posterior segments of the eye (i.e. panuveitis). Moreover, these results suggested that Zone III, or peripheral, lesions were more common in older patients in these cohorts. Of note, heavy venous exudation, or so-called ''candle-wax-like drippings,'' thought to be highly suggestive for ocular sarcoidosis, were only identified in four patients (4.8%). The authors speculated that sex-related differences in hormones, such as testosterone, may have contributed to the increased prevalence of ocular sarcoidosis in older woman, and perhaps the age-related differences in lesion location, but provide no mechanistic explanation as to how varying hormone levels might produce such gender- and age-related differences. Previous cross-cohort comparisons have suggested the possibility of differences in severity and location of sarcoid uveitis based on race and age.[6–16]

Güngör et al. used enhanced depth imaging (EDI) optical coherence tomography (OCT) to evaluate the choroidal thickness at and within 3000 microns of the fovea in 18 eyes of nine patients with quiescent, biopsy-proven ocular sarcoidosis seen in a uveitis referral clinic in Ankara, Turkey.[21] One patient with quiescent ocular sarcoidosis was receiving low-dose systemic methylprednisolone to control pulmonary disease at the time of the study. As in the study by Nagata et al., patients with ocular sarcoidosis tended to be female (88.9%) and older, with an overall mean age in the cohort of nearly 60 years. On average, the total duration of active uveitis was 5.6 years (range 2–12 years; SD ± 4.1 years) and the mean duration of remission prior to EDI OCT measurement was 1.9 years (range 1–3 years; SD ± 0.8 years). Choroidal thickness measurements from nine healthy age-matched subjects, including six women and three men, were used as controls. Inactive posterior segment lesions noted at the time of EDI OCT included perivascular gliosis (8/9; 88.8%), focal chorioretinal scarring (6/9; 66.7%), and chorioretinal folds (1/9; 11.1%). As expected, imaging revealed the choroid to be thickest just beneath the fovea in both patients with quiescent ocular sarcoidosis and age-matched healthy controls. The mean thickness of the choroid was thicker in control patients at all locations tested; a difference that achieved approximately 20% immediately below the fovea. Wolfensberger and Herbort[24] used ICGA to show a high rate of choroidal involvement in patients with ocular sarcoidosis, despite the fact that the vast majority had no clinical or fluorescein angiographic evidence of inflammation in the choroid.[25] Several groups have described reversal of choroidal thickening, and even atrophy, in patients with VKH disease following treatment.[26–30]

Hessen et al. described a 58-year-old black woman who developed a painless 6×7 mm scleral nodule underneath normal appearing conjunctiva with no clinical evidence of scleral inflammation.[21] At the time of biopsy, the lesion was found to arise from the sclera and to involve the insertion of the medial rectus muscle. In addition, several elevated, indurated, and hypopigmented plaques were present on the left side of her nose and on her cheeks. Biopsy of both the scleral nodule and a selected skin lesion revealed findings consistent with sarcoidosis, including non-caseating granulomas with giant cells. The patient was placed on systemic prednisone and hydroxychloroquine together with topical cyclosporine to treat the scleral lesion and corticosteroid cream for the skin lesions. When no improvement was seen in the scleral and skin lesions following 4 months of treatment, triamcinolone acetonide injections were given for the skin lesions and consideration was given to adding systemic methotrexate. While scleral involvement has been reported previously in patients with sarcoidosis,[30–32] there was, in each case, evidence of inflammation of the sclera, or scleritis, as opposed to the painless nodule noted in this patient.

Finally, Psaltis et al. described a 44-year-old African American man who developed moderate to severe bilateral granulomatous anterior uveitis associated

with thickening of red-dye areas of a 10-year-old multi-colored tattoo – both coincident with receipt of an intramuscular influenza vaccination.[22] The uveitis was complicated by extensive posterior synechiae formation, followed within 6 months by the development of cystoid macular edema. Systemic evaluation revealed an elevated serum ACE level and mediastinal lymphadenopathy with mild airway restriction on functional testing. A punch biopsy of the red dye portion of the involved tattoo showed dense lichenoid granulomatous inflammation, including multi-nucleated giant cells. Biopsy of the lung lesions confirmed sarcoidosis and, of note, showed no evidence of red dye particles. The vaccine given to the patient contained thimerosal preservative, known to contain mercury. Mercury, in the form of mercuric sulfide, was also used in older red tattoo dyes, leading the authors to speculate that the granulomatous inflammation in both the eyes and at the site of the red dye tattoo ink may have been triggered by the vaccine. Handler et al. reported a similar case following H1N1 influenza vaccine, but limited to blue dye areas.[33] Psaltis et al. provided a detailed summary of over 30 previously reported cases of granulomatous reaction to various tattoo dye colors, approximately one-third of which were associated with uveitis. Ostheimer et al. recently reported tattoo-associated uveitis in a series of seven patients seen at The Wilmer Eye Institute over an 18-month period.[34] Six of the seven patients were African American and four were male. All seven patients had bilateral uveitis, including five with non-granulomatous anterior uveitis, four chronic and one recurrent, and two with chronic granulomatous panuveitis. One patient had an elevated serum ACE level and a second an elevated serum lysozyme level. Two patients had regional lymphadenopathy near tattoos. Five of the seven affected tattoos had only black ink, and only the black ink portion of the remaining two multi-color tattoos was affected. Biopsy was performed on two involved tattoos and revealed non-caseating granulomas composed of histiocytes. Anti-inflammatory treatments included topical corticosteroids alone in one patient, systemic corticosteroids alone in one patient, both topical and systemic corticosteroids in two patients, and topical and systemic corticosteroids plus an anti-metabolite in three patients. Five of the seven patients developed posterior synechiae in one or both eyes, including iris bombe formation in three eyes. Four patients required intraocular pressure lowering drops and one patient required bilateral Baerveldt valve placement.

Together, these four studies further characterize ocular complications of sarcoidosis and of tattoo-associated uveitis – which appears to be sarcoid-like in many respects. The fact that granulomatous skin and ocular inflammation closely followed influenza vaccination in the patients with tattoo-associated uveitis reported by Psaltis et al. in this issue of *OII*,[22] and by Handler et al. in a previous publication,[33] supports the notion that environmental triggers may be important to the pathogenesis of both systemic and ocular sarcoidosis.[35]

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DECLARATION OF INTEREST

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