Tattoo-Associated Uveitis

TRUCIAN A. OSTHEIMER, BRYN M. BURKHOLDER, THERESA G. LEUNG, NICHOLAS J. BUTLER, JAMES P. DUNN, AND JENNIFER E. THORNE

• PURPOSE: To describe the clinical presentation of uveitis with coincident onset of raised and indurated tattooed skin.
• DESIGN: Case series.
• METHODS: Seven consecutive patients were evaluated at a tertiary ophthalmologic facility with coincident uveitis and cutaneous tattoo induration over an 18-month period. All subjects underwent complete ophthalmic examination and a focused systemic medical evaluation including serologic testing and imaging studies. Two participants underwent biopsy of their tattoos. The patients’ clinical courses and responses to treatment over a follow-up period of 1–20 months are reported (mean follow-up = 9 months). Main outcome measures included degree of intraocular inflammation, ocular complications, visual acuity, clinically observable tattooed skin changes, and biopsy results.
• RESULTS: Five of 7 patients had bilateral nongranulomatous anterior uveitis; 4 with chronic and 1 with recurrent disease. The remaining 2 patients had bilateral chronic granulomatous panuveitis. Biopsies of raised and indurated tattoos were performed in 2 patients and demonstrated noncaseating granulomatous inflammation surrounding tattoo ink in the dermis. The skin changes resolved in all patients, with a faster response noted in those treated with high-dose oral prednisone for intraocular inflammation. Five patients subsequently experienced recurrent flares of intraocular inflammation in conjunction with the recurrence of raised and indurated tattoos.
• CONCLUSIONS: These cases represent a subset of patients in whom skin tattooing may have incited an immune response leading to simultaneous inflammation of the eyes and tattooed skin. (Am J Ophthalmol 2014;158:637–643. © 2014 by Elsevier Inc. All rights reserved.)

In 1952, LUBECK AND EPSTEIN PUBLISHED THE FIRST report of a patient with bilateral intraocular inflammation and simultaneous tattoo granulomas in the setting of systemic sarcoidosis.1 This was followed, in 1969, by the first case series to describe bilateral intraocular inflammation with the simultaneous development of tattoo granulomas in 3 patients felt to have no evidence of systemic sarcoidosis at the time of presentation.2 The pathologic hallmark of sarcoidosis is the noncaseating granuloma; however, it remains a diagnosis of exclusion because of its lack of pathognomonic histopathology, imaging, or serologic studies.3 Among patients with sarcoidosis, anywhere from 25% to 80% may suffer from ocular or adnexal involvement,4 and approximately 25%–35% of patients develop cutaneous findings.5 Anterior uveitis is the most common ocular manifestation of sarcoidosis, occurring in 65% of patients with ophthalmic involvement.6

We present 7 patients with no prior diagnosis of sarcoidosis who developed bilateral uveitis in temporal association with inflammation of tattooed skin.

METHODS

A RETROSPECTIVE REVIEW OF 7 CONSECUTIVE PATIENTS with bilateral uveitis and associated cutaneous changes suggestive of tattoo inflammation evaluated over a 20-month period was conducted at the Division of Ocular Immunology, Wilmer Eye Institute. The study was approved by the Johns Hopkins School of Medicine Institutional Review Board and adhered to all tenets of the Declaration of Helsinki. All patient data were handled in accordance with the Health Information Portability and Accountability Act.

All patients underwent a complete ophthalmologic examination and received a medical evaluation (Table) in an attempt to rule out syphilis (fluorescent treponemal antibody-absorption [FTA-ABS] and rapid plasma reagin testing [RPR]) and sarcoidosis (chest x-ray and/or computed tomography [CT] chest, serum angiotensin-converting enzyme [ACE] and/or serum lysozyme). Testing for HLA-B27 positivity and infectious etiologies such as Mycobacterium tuberculosis, Toxoplasma gondii, Bartonella henselae, and Borrelia burgdorferi was performed in selected patients. Two of the 7 patients underwent biopsy of their inflamed tattoos. The patients’ clinical courses and responses to treatment were reviewed over a follow-up period of 1–20 months.

• SELECTED CASE REPORT: PATIENT 1: Patient 1 was a 20-year-old African-American man who initially presented for

Accepted for publication May 16, 2014.
From Wilmer Eye Institute, Johns Hopkins University School of Medicine (T.A.O., B.M.B., T.G.L., N.J.B., J.P.D., J.E.T.); and Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University (J.E.T.), Baltimore, Maryland.
James P. Dunn is currently employed at the Wills Eye Institute, Philadelphia, Pennsylvania.
Inquiries to Trucian A. Ostheimer, Wilmer Eye Institute, 600 N Wolfe St, Woods 476, Baltimore, MD 21287; e-mail: tosthei1@jhmi.edu

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<table>
<thead>
<tr>
<th>Patients Demographics</th>
<th>Initial VA</th>
<th>Intraocular Inflammation</th>
<th>Uveitic Evaluation$^a$</th>
<th>Sarcoïdosis Evaluation$^a$</th>
<th>Tattoo Findings</th>
<th>Tattoo Biopsy</th>
<th>Ocular Complications</th>
<th>Treatment</th>
<th>Follow-up Duration</th>
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<tr>
<td>1 20yo AAM OD(sc): 20/100, OS(sc): 20/400; PHNI OU</td>
<td>Bilateral granulomatous chronic panuveitis</td>
<td>RPR, FTA-ABS, HLA-B27, IGRA, Lyme serology, Toxoplasma IgG, CMP, CBC</td>
<td>ACE, chest x-ray ($\times 2$)</td>
<td>Elevation/induration of skin tattooed with black pigment (predominantly black tattoos on arms, chest, and abdomen)</td>
<td>Noncaseating granulomatous reaction associated with tattoo ink</td>
<td>OU: posterior synechiae, glaucoma s/p Baerveldt glaucoma implants</td>
<td>Mycophenolate mofetil, oral prednisone, topical corticosteroids, and IOP-lowering drops</td>
<td>13 months</td>
<td></td>
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<tr>
<td>2 31yo WM OU</td>
<td>Bilateral nongranulomatous recurrent anterior uveitis</td>
<td>RPR, FTA-ABS, HLA-B27, PPD, CMP, CBC</td>
<td>ACE, lysozyme, chest x-ray, CT chest, lymph node biopsy$^b$</td>
<td>Elevation/induration of skin tattooed with black pigment (multicolored, extensive tattoos on both arms)</td>
<td>Noncaseating granulomatous reaction associated with tattoo ink</td>
<td>OU: steroid-associated ocular hypertension</td>
<td>Topical corticosteroids, IOP-lowering drop</td>
<td>17 months</td>
<td></td>
</tr>
<tr>
<td>3 32yo AAM OU(sc): 20/25-2; PHNI OU</td>
<td>Bilateral nongranulomatous chronic anterior uveitis</td>
<td>RPR, FTA-ABS, HLA-B27, Lyme serology, CMP, CBC</td>
<td>ACE, chest x-ray</td>
<td>Elevation/induration of skin tattooed with black pigment on both arms (black tattoos on chest never involved)</td>
<td>Not performed</td>
<td>OU: pupillary membranes, cataracts, CME</td>
<td>Methotrexate, oral prednisone, topical corticosteroids, IOP-lowering drops</td>
<td>20 months</td>
<td></td>
</tr>
<tr>
<td>4 23yo AAF OD(sc): 20/40, OS(sc): 20/200-2; PHNI OU</td>
<td>Bilateral nongranulomatous chronic anterior uveitis</td>
<td>RPR, FTA-ABS, HLA-B27, Lyme serology, CMP, CBC</td>
<td>Lysozyme, chest x-ray</td>
<td>Elevation, induration, and scaling of tattoos with black ink (multicolored tattoos on face, neck, torso, back, and all limbs)</td>
<td>Not performed</td>
<td>OU: posterior synechiae, pupillary membranes, iris bombe, severe CME OS: uveitic glaucoma</td>
<td>Mycophenolate mofetil, oral prednisone, topical corticosteroids, IOP-lowering drops</td>
<td>7 months</td>
<td></td>
</tr>
<tr>
<td>5 23yo AAM OD(sc): 20/25, OS(sc): 20/20 - 1; PHNI OU</td>
<td>Bilateral nongranulomatous chronic anterior uveitis</td>
<td>RPR, FTA-ABS, HLA-B27, Lyme serology, CMP, CBC</td>
<td>ACE, chest x-ray</td>
<td>Elevation/induration of skin tattooed with black pigment (black tattoos on arms/ chest)</td>
<td>Not performed</td>
<td>OS: posterior synechiae</td>
<td>Topical corticosteroids</td>
<td>4 months</td>
<td></td>
</tr>
<tr>
<td>6 21yo AAF OD(sc): 20/100, OS(sc): 20/40; PH 20/80 OD, PHNI OS</td>
<td>Bilateral nongranulomatous chronic panuveitis with hypopyon</td>
<td>RPR, FTA-ABS, HLA-B27, PPD, Lyme serology, Bartonella antibody panel, CMP, CBC</td>
<td>ACE, chest x-ray</td>
<td>Elevation/induration of skin tattooed with black pigment (multicolored tattoos on back)</td>
<td>Not performed</td>
<td>OU: severe optic nerve elevation and hyperemia with papillomacular exudates, ERM OD: subfoveal RPE detachment</td>
<td>Oral prednisone, topical corticosteroids</td>
<td>2 months</td>
<td></td>
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The following table presents patient demographics and findings in tattoo-associated uveitis (Continued):

<table>
<thead>
<tr>
<th>Patients</th>
<th>Demographics</th>
<th>Initial VA</th>
<th>Intracocular Inflammation</th>
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<th>Tattoo Findings</th>
<th>Tattoo Biopsy</th>
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<th>Treatment</th>
<th>Follow-up Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>42yo AAM</td>
<td>OD(sc): 20/20, 0.8(scl): 20/40, PHN: OD, PH OS: 20/32</td>
<td>Bilateral nongranulomatous chronic anterior uveitis</td>
<td>FTAA-ABS, HLA-B27, CMP, CBC, ACE, lysozyme, chest X-ray, CT chest</td>
<td>Elevation/induration of skin tattooed with black pigment (arm)</td>
<td>Not performed</td>
<td>OU: posterior synechiae</td>
<td>OD: neurosensory retinal detachment</td>
<td>Oral prednisone; systemic immunosuppression recommended</td>
<td>1 month (last to follow-up)</td>
</tr>
</tbody>
</table>

AAF = African-American female; AAM = African-American male; ACE = serum angiotensin-converting enzyme; CBC = complete blood count; CME = cystoid macular edema; CMP = complete metabolic panel including liver function testing; CT = computed tomography; ERM = epiretinal membrane; FTAA-ABS = syphilis fluorescent treponemal antibody-absorption; IgG = immunoglobulin G; IGRA = interferon gamma release assay (QuantiFERON–TB Gold); IOP = intraocular pressure; PH = visual acuity measured with pinhole occluder; PHNI = visual acuity measured with pinhole occluder offered no improvement in vision; PPD = tuberculosis purified protein derivative skin testing; RPE = retinal pigment epithelium; RPR = syphilis rapid plasma regain; sc = without correction; VA = visual acuity; WM = white male; yo = year old.

aAll results unremarkable/negative unless otherwise indicated.

bPatient 2 underwent biopsy of an enlarged axillary lymph node, which displayed a noncaseating granulomatous reaction. Patient 6 had an elevated ACE value of 85 (reference range: 9–67 U/L).

Patient 7 had an elevated lysozyme value of 32 (reference range: 9–17 μg/mL) and a normal serum ACE value of 47.

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containing black ink. Punch biopsies of the affected skin were taken from his left shoulder and chest. Histology slides of these biopsy specimens revealed aggregates of epithelioid histiocytes and giant cells containing pigment particles with sparse mononuclear cell infiltrate (Figure 1).

Ultimately, his refractory ocular hypertension resulting from a combination of uveitic and steroid response mechanisms required placement of glaucoma drainage devices 4 months and 6 months after presentation in the right and left eye, respectively. The patient agreed to initiation of immunosuppressive therapy with mycophenolate mofetil, which enabled successful tapering of oral prednisone. At the most recent examination, 13 months after presentation, BCVA was 20/25 bilaterally with controlled IOP and intraocular inflammation on mycophenolate mofetil 1.5 g twice daily and prednisone 5 mg once daily.

### RESULTS

**SELECTED CLINICAL CHARACTERISTICS OF ALL 7 PATIENTS** are summarized in the Table. Six patients were African Americans, 4 of whom were male. The remaining patient was a white man. The age range of all patients was 20–42 years at the time of presentation. Five patients presented with bilateral nongranulomatous anterior uveitis, while the remaining 2 patients presented with granulomatous panuveitis. One patient with anterior uveitis had recurrent disease, while all other patients had chronic uveitis.

A medical examination was performed on all patients and interpreted as unremarkable, with the exception of a single elevated serum ACE (Patient 6) and lysozyme value (Patient 7). Patient 4 presented with submandibular and occipital lymphadenopathy not associated with overlying tattooing, though she did have extensive head and neck tattoos. Patient 2 developed an enlarged left axillary lymph node near the area of heavy tattooing on the same arm.

All patients denied abnormal cutaneous reactions immediately after tattooing, and all had their most recent tattoo placed at least 6 months prior to the onset of cutaneous and intraocular symptoms. Five of the patients had extensive tattoos, all of which consisted entirely of only black pigment or multicolored tattoos containing black ink. The remaining 2 patients had more limited tattooing (Patients 6 and 7). Only tattoos or portions of tattoos containing black pigment were affected in all 7 patients. Involvement of the affected tattoos varied from focal nodular elevation in regions of black pigment to uniform elevation and induration of all portions of the tattoo containing black ink (Figure 2). In Patient 1, striking elevation and induration of the surrounding skin was also observed. Five patients (Patient 1 and Patients 3–6) experienced at least 1 recurrence of intraocular inflammation with simultaneous tattoo involvement.
Tattoo biopsies were performed on Patients 1 and 2. A tattoo biopsy on Patient 2 was performed 2 weeks prior to presentation and displayed noncaseating granulomas composed of histiocytes surrounding black tattoo pigment in the dermis. His enlarged axillary lymph node also was biopsied and displayed noncaseating granulomatous inflammation. Similar findings were demonstrated in the tattoo biopsies of Patient 1. Patients 4 and 5 were referred for biopsy of their tattoos and enlarged lymph nodes (Patient 4) immediately after their initial evaluation, but both failed to follow up with dermatology and had rapid resolution of these findings following initiation of high-dose oral prednisone. The remaining patients (Patients 3, 6, and 7) were not sent for biopsy of their involved tattoos because they were immediately treated with high-dose oral prednisone, which coincided with rapid resolution of their tattoo findings over the course of approximately 1 week. Owing to military service obligations requiring him to relocate, Patient 7 was lost to follow-up after 2 visits.

Five of 7 patients suffered potentially vision-threatening ocular complications at some point during observation. Patients 3 and 4 presented with iris bombe, pupillary membranes, and cystoid macular edema, which subsequently required treatment with immunosuppressive therapy. Patient 7 presented to our institution with a neurosensory retinal detachment in the right eye and severe cystoid macular edema in the left eye. All patients treated with oral prednisone (Patients 1, 3, 4, 6, and 7) displayed simultaneous improvement in their ocular inflammation and resolution of their tattoo findings.

DISCUSSION

WE DESCRIBE A SERIES OF 7 CONSECUTIVE PATIENTS WHO demonstrated simultaneous onset of bilateral uveitis and tattoo elevation with induration. Five other cases published in 3 articles reported similar findings and no additional evidence of sarcoidosis on examination or chest imaging (chest x-ray and/or CT studies) at the time of presentation.2,5,6 Similar to our series, these 5 patients exhibited bilateral uveitis, ranging from iridocyclitis to panuveitis. During observed follow-up, 1 patient developed “red infiltrates resembling erythema nodosum” on both shins that were not associated with tattooed skin.2 In our series, Patient 2 developed noncaseating granulomatous inflammation of an axillary lymph node adjacent to an area of dense tattooing, and Patient 3 developed submandibular and occipital lymphadenopathy, which was suspicious for sarcoidosis. Furthermore, there have been cases reported in the literature of patients with a diagnosis of systemic sarcoidosis at the time of presentation with bilateral uveitis and tattoo induration.1,7,8

Each of the patients in our series had extensive areas of tattooing that contained or consisted entirely of black ink. Other published reports describe skin inflammation associated with blue,7 red,5 and black ink.6–8 Tattoo size and color varied, although 1 case report described a patient with extensive black tattooing,6 which was similar to the patients in our series. All of our patients received the majority of their tattoos over a relatively short period of time—approximately 1 year or less—but none experienced induration or inflammation of the tattoos at the time of tattoo placement. In the majority of reports, the inflammation of tattooed skin coincided with the onset of uveitis except for 2 of 3 patients reported by Rorsman and associates, in whom tattoo inflammation occurred immediately after placement and did not correlate temporally with their delayed ocular involvement.7

Of the 8 previously reported patients with tattoo-associated uveitis, 4 underwent complete excision of the affected tattoo(s).2,5 Interestingly, 3 of these 4 patients were reported to have improvement in their intraocular inflammation following tattoo excision, with 2 achieving complete resolution off of all medications. As with our series, the follow-up periods in these cases were limited, and it remains unclear whether tattoo excision had a role in disease resolution or simply coincided with spontaneous disease remission. Unlike these previously reported cases, tattoo excision was not offered to the patients we continue to follow at our facility, as the percentage of body surface area encompassed by their involved tattoos was deemed too extensive for subsequent skin grafting.

Various patterns of histologic reactions have been reported to occur in tattooed skin, and one of the more common findings is granulomatous inflammation.4 Histologically, this can be classified as a foreign body or sarcoid-type reaction, and the
differences of these 2 types of granulomas may be both challenging and open to controversy. 9,10 Allergic reactions to tattoo pigment can also occur, which may exhibit a variety of histologic forms, some of which are also consistent with sarcoidosis. 9 Granulomatous reactions confined to single tattoo colors typically represent a local hypersensitivity reaction to specific components of tattoo pigment, but they may also represent a manifestation of systemic sarcoidosis. 9 Interestingly, reports of allergic reactions to black tattoo pigment are very rare. 11 The histologic appearance of tattoo biopsy specimens obtained from 2 of the 7 patients in our series were interpreted as noncaseating granulomatous inflammation in association with dermal tattoo pigment, which is consistent with but not specific for sarcoidosis.

Although the etiology of sarcoidosis remains unclear, it is hypothesized that the disease process is initiated when a genetically susceptible host is exposed to an inciting environmental antigen(s). 3,10 In such an event, an exaggerated immune response characterized by the activation of macrophages and CD4+ T lymphocytes occurs, resulting in cytokine production consistent with a TH1-type immune response, ultimately leading to granuloma formation. 3,10 Considering the multiple environmental risk factors reported to date, it seems reasonable to conclude that the development of sarcoidosis is likely the end result of immune responses to a potentially large variety of environmental triggers. 3,4

The production of black tattoo ink is based on soot, which may “contain toxic, mutagenic or carcinogenic compounds such as carbon black and polycyclic aromatic hydrocarbons or phenol.” 12 Carbon black nanoparticle exposure in lung cell lines 13 and mice 14 have shown that these particles “induce inflammation, oxidize DNA, cause DNA strand breaks and increase the mutant frequency following long-term exposure at a subcytotoxic concentration.” 15 All of our patients received the majority of their tattoos over a relatively short period of time—approximately 1 year or less—which may have conferred an increased risk of disease development as a result of the relatively large antigenic and/or toxic load. Interestingly, the US Food and Drug Administration has not approved any tattoo pigments for injection into the skin, and many pigments used in tattoo inks are industrial-grade colors suitable for printers’ ink or automobile paint. 16 Among adults 18–50 years of age in this country, the prevalence of tattoos may be as high as 24%. 17

Ultimately, the patients in our series seem to represent a subset of patients in whom some component of tattoo pigment initiated a localized cutaneous response that by some means also played a role in the simultaneous development of ocular inflammation. Whether the pathophysiology of this process is similar to systemic sarcoidosis, is the result of a hypersensitivity response, or is attributable to some other mechanism is not yet known. Continued observation for the development of additional organ system involvement consistent with sarcoidosis, and the potential benefit of tattoo removal, if performed, may be useful knowledge. Altogether, the clinical presentation of the patients collected for this series nearly equals the cumulative number of previously reported cases, suggesting that this association is likely underappreciated.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST. Jennifer E. Thorne discloses the following: grant funding from the National Institutes of Health (Bethesda, Maryland, USA), Research to Prevent Blindness Sybil B. Harrington Special Scholar Award (New York, New York, USA), Allergan (Irvine, California, USA); consultant for AbbVie (North Chicago, Illinois, USA), Gilead (Foster City, California, USA), Navigant (Chicago, Illinois, USA), Xoma (Berkeley, California, USA). The authors indicate no funding support. Contributions of authors: all listed authors made substantial contributions regarding (1) data acquisition (T.O., B.B., T.L., N.B., J.D., J.T.); (2) drafting (T.O.) or revising the article (T.O., B.B., T.L., N.B., J.D., J.T.); and (3) approval of submitted version (T.O., B.B., T.L., N.B., J.D., J.T.).

Pathology consultation was provided by Gulsun Erdag, MD, Johns Hopkins School of Medicine, Baltimore, Maryland, USA.

REFERENCES


Biosketch

Trucian Ostheimer, MD, graduated from the Ohio State University College of Medicine in 2008, and completed his ophthalmology residency at the Illinois Eye & Ear Infirmary in 2012. He is currently completing a two-year ocular immunology fellowship at the Wilmer Eye Institute, and has a special interest in birdshot chorioretinopathy. Dr Ostheimer will begin a fellowship in vitreoretinal surgery at the University of Washington in July, 2014.