Cutaneous Sarcoidosis treated with Retinoids: A Case Report and Review of Nine Cases

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ABSTRACT

Background: Sarcoidosis is a noncaseating granulomatous disease that affects multiple systems, including the skin. Treatment for cutaneous sarcoidosis is varied and mostly based on anecdotal knowledge from the literature. The commonest treatment for cutaneous sarcoidosis involves topical, intralesional, and/or systemic corticosteroids. Other treatments, including retinoids, have been trialed with varying response.

Case presentation: A 71-year-old female had been diagnosed with cutaneous sarcoidosis when she was 59 years old. She was initially treated with corticosteroids, followed by methotrexate until the age of 68 years, at which point she was switched to acitretin due to failure of resolution on the previous treatment. The patient's condition improved dramatically within 8 months of treatment.

Conclusion: A literature review identified eight other cases of cutaneous sarcoidosis treated with retinoids (isotretinoin in six cases and etretinate in two cases). Of these cases, only one responded unfavorably, whereas resolution was seen within 8 months in the other seven cases, similar to our case. This suggests that retinoids may be a potential treatment option for cutaneous sarcoidosis, possibly owing to their anti-inflammatory and immunomodulatory properties.

Keywords: Retinoids, acitretin, granuloma, recalcitrant cutaneous sarcoidosis, case report.

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Background

Sarcoidosis is a granulomatous disease that can affect multiple organ systems, including skin (in around one-fourth of cases), lungs, liver, eyes, heart, and lymph nodes [1]. The typical histological features, including noncaseating epithelioid granulomas, help to distinguish sarcoidosis from other granulomatous diseases, such as tuberculosis [2].

The cause of cutaneous sarcoidosis is debated but possibly involves a T-cell-mediated immune response to infective or environmental antigens, and/or genetic factors, which lead to activation of lymphocytes and macrophages and granuloma formation [1,3]. Increased production of TNF from macrophages and decreased production of prostaglandin E2 may also occur [2].

Although cutaneous sarcoidosis is not life-threatening, lesions are often unsightly and cosmetically distressing [1]. The current treatment options are limited, not very effective, and based mostly on anecdotal knowledge from case reports and small series in the literature [3]. We report a patient whose long-standing cutaneous sarcoidosis responded impressively to the retinoid acitretin, after minimal response to corticosteroids and methotrexate. To our knowledge, this is the first report of successful treatment of cutaneous sarcoidosis with acitretin.

Case Presentation

A Caucasian lady was diagnosed with cutaneous sarcoidosis in 2010 at 59 years of age. Initially, she had presented with a 1-year history of prominent erythemato-violaceous nodular infiltrates on the forehead over the glabella and above the left eyebrow, on the right ear lobe, and nose (Figure 1). There was no history of erythema nodosum.

A skin biopsy showed noncaseating granulomatous inflammation in keeping with cutaneous sarcoidosis.

The patient was also noted to have right axillary lymphadenopathy, which was further investigated with a CT scan of the thorax. This revealed extensive lymphadenopathy in the neck, axillary fossae, mediastinum, abdomen, retroperitoneal space, pelvis, and both groins. Given her history of left-sided breast cancer in remission, the patient underwent axillary lymph node biopsy, which showed complete effacement of parenchyma by non-necrotizing

epithelioid discrete sarcoid-type granulomas, with no signs of malignancy.

Other investigations including complete blood counts, serum calcium, serum angiotensin converting enzyme, immunology screen, and lung function testing were within normal limits.

Initial treatment of the skin lesions with clobetasol propionate ointment produced no noticeable improvement after 2 years and the involved areas became more prominent. A trial of acitretin (Neotigason®) 20 mg daily was given in 2012 for a few months; however, compliance with treatment was poor. During this time, the lesions flattened but remained noticeable and the patient declined further treatment. In June 2013, the patient requested further treatment and methotrexate was started with the dose increased gradually to 15 mg weekly. On this treatment, the lesions again improved only slightly. The papular areas on the forehead and right ear were additionally treated with intralesional methylprednisolone, with limited response.

The patient continued methotrexate and was monitored with regular routine blood tests, type 3 procollagen peptide and liver elastography. Methotrexate was stopped in 2019 when F2 liver fibrosis was detected on elastography. By now, the patient was 68 years old, and treatment had produced only minimal improvement of her condition. At this point, it was decided to retry acitretin, initially at 10 mg daily, increased to 20 mg daily after 2 months. The importance of compliance to treatment with acitretin was emphasized to the patient.

There was dramatic improvement, and the lesions flattened almost completely within a few months and erythema became much less noticeable. Acitretin was well tolerated; however, some diffuse, likely drug-induced alopecia, developed and therefore the acitretin dose was reduced back to 10 mg daily and the alopecia resolved.

A recent ultrasound of axillae revealed unchanged lymphadenopathy and recent chest X-ray was clear. The patient is currently still on acitretin 10 mg daily and doing very well from both a medical and an aesthetic point of view (Figure 2).

Discussion

Evidence-based data on treatment of cutaneous sarcoidosis is lacking, and the current treatment options are based on anecdotal knowledge from case reports or extrapolated from treatment used in pulmonary sarcoidosis [4]. Traditionally, topical, intralesional, or systemic corticosteroids are first-line therapy and widely used. Other reported treatments include allopurinol, methotrexate, hydroxychloroquine, and, more recently, TNF-alpha inhibitors, such as infliximab. Unfortunately, the efficacy of these treatments is mostly modest [3]. Retinoids may be another treatment option for cutaneous sarcoidosis, and we were aware of some published reports where retinoids have been used when prior treatment yielded unsatisfactory results or adverse effects.

We performed an extensive literature search to collate all reported cases of cutaneous sarcoidosis treated with retinoids and provide a summary of their details, including patient demographics, initial treatment prescribed, type and dose of retinoid used, and any adverse effects. PubMed and Google Scholar were used to search for cases using the terms “cutaneous sarcoidosis” and “retinoids.”

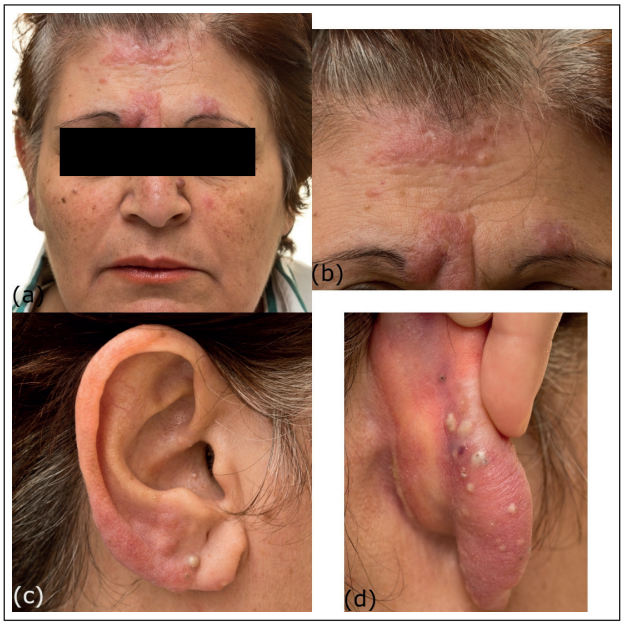

Figure 1. *Erythemato-violaceous nodular infiltrates over the glabella, above the left eyebrow, and on the right pinna, taken in 2013.*

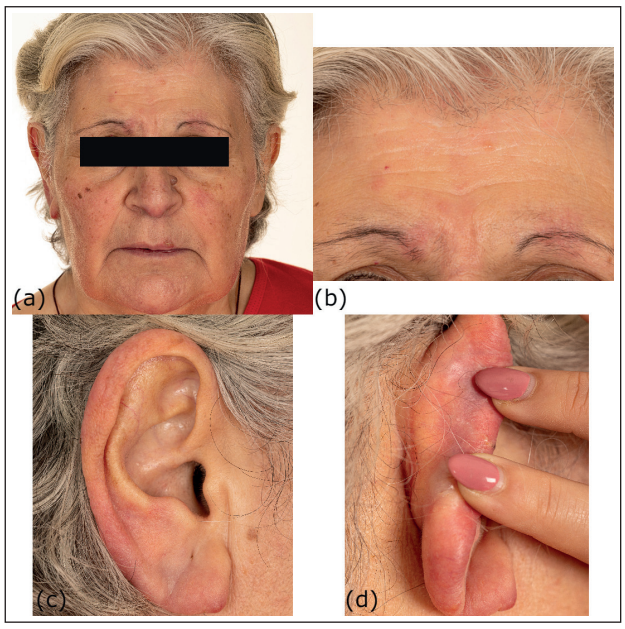

Figure 2. *The patient’s face and right ear with dramatic improvement, taken in 2021.*

In total, eight case reports of cutaneous sarcoidosis treated with retinoids were found, making our case the ninth reported case. The cases are summarized in Table 1.

Of the cases identified, six were female, two were male, and in one case gender was not stated. Mean age was 37.86 years (range 22-68 years); however, in two cases, age was not given. The patients were initially treated with corticosteroids, followed by other treatments like allopurinol, antimalarials, and methotrexate. In three cases, initial treatment was not stated. Isotretinoin was the retinoid prescribed in six of the nine cases; etretinate in two cases; and acitretin in one (our) case. To our knowledge, there are no other reports of acitretin used to treat cutaneous sarcoidosis. Improvement of clinical condition was achieved in 4-8 months on retinoid treatment. Only one case reported an unfavorable outcome, which led to stopping of the retinoid after 7 weeks. Outcome was not stated in one case.

Retinoids are vitamin A derivatives that are established treatments for several dermatological conditions (Table 2). Historically, etretinate was withdrawn from most markets in the 1990s in view of its long half-life of 80-160 days and a narrow therapeutic index. Both cases treated with etretinate included in our literature review occurred prior to 1990. Instead of etretinate, a newer second-generation retinoid, acitretin, which is a metabolite of etretinate with a much shorter half-life of 50-60 hours, was introduced. Isotretinoin was the commonest choice of retinoid in our literature review, possibly because isotretinoin has a much more favorable shorter half-life of approximately 20 hours [12, 13]. In our patient, we opted for acitretin based on our experience in its use to treat chronic skin conditions, such as psoriasis, ichthyosis, and Darier disease, among others.

Retinoids are known to have anti-inflammatory and immunomodulatory properties, yet their mechanism in the context of cutaneous sarcoidosis is poorly understood

Table 1. *Reported cases of cutaneous sarcoidosis treated with retinoids.*

CASE	SEX	AGE (YEARS)	INITIAL TREATMENT PRESCRIBED	RETINOID PRESCRIBED	TREATMENT REGIME	OUTCOME	ADVERSE EFFECTS
Waldinger et al. [5]	F	39	Corticosteroids, allopurinol	Isotretinoin	40 mg/day, increased to 80 mg/day at week 7, decreased to 40 mg/day at week 16, stopped at 30 weeks	No further regression of skin lesions at 30 weeks; 75% regression of peripheral lymphadenopathy	Myalgia, Chelitis
Spiteri and Taylor [6]	F	33	Corticosteroids	Etretinate	25 mg three times/day, decreased to 25 mg twice/day at week 3, stopped at week 7	Worsening of lesions	Cheilitis, exfoliative dermatitis
Vaillant et al. [7]	F	NS	Corticosteroids, allopurinol, antimalarials	Isotretinoin	0.4-1.0 mg/kg/day for 6 months	Complete response in one lesion, partial improvement in the other skin lesion	NS
Claudy [8]	NS	NS	NS	Etretinate	NS	NS	NS
Georgiou et al. [2]	F	31	Corticosteroids, hydroxychloroquine	Isotretinoin (Roaccutane®)	1 mg/kg/day for 8 months	Complete resolution by 8 months	Chelitis, xerosis, Nasal mucosa dryness
Chong et al. [9]	M	22	NS	Isotretinoin	NS	Partial improvement	NS
Mosam and Morar [10]	F	41	Corticosteroids, allopurinol, azathioprine	Isotretinoin	25 mg/day for 6 months	Complete response	NS
Choi et al. [11]	M	31	NS	Isotretinoin	20 mg/day for 4 months	Complete remission	NS
Farrugia and Boffa (2022)	F	68	Corticosteroids, methotrexate	Acitretin (Neotigason®)	10 mg daily ×2 months, then 20 mg daily × 4 months, then 10mg/20 mg daily × 6 months, then 10 mg daily (to present day)	Complete response	Alopecia

M = male, F = female, NS = not stated.

Table 2. *Systemic retinoids used in dermatology [12].*

GENERATION OF RETINOID	NAME	MAIN INDICATION(S)
First generation	Isotretinoin	Acne
	Alitretinoin	Hand eczema
Second generation	Etretinate[a]	
	Acitretin	Psoriasis, disorders of keratinization, e.g., ichthyosis
Third generation	Bexarotene	Cutaneous T-cell lymphoma

[a] Withdrawn from most markets in the 1990s.

[14]. It has been proposed that retinoids may inhibit T cell mediated immunity immunity by increasing the activity of prostaglandin E2 and by decreasing tumor necrosis factor activity, which may lead to downregulation of granuloma formation [2,3]. One experimental study conducted by Kim et al. [14] showed that all trans-retinoic acid induced the production of prostaglandin E2 in brain microglia of mice. This increase of E prostaglandins inhibited granuloma formation. Another study conducted by Mehta et al. [15] showed that all trans-retinoic acid inhibited tumor necrosis factor-α in mice peritoneal macrophages. By binding to retinoic acid receptors, retinoids are then able to exert their effects, and this may explain the mechanism behind the therapeutic action of retinoids in cutaneous sarcoidosis.

Retinoids are generally well tolerated. Their side effect profile is well known and includes xerosis, cheilitis, hyperlipidemia, and teratogenicity [3]. With respect to teratogenicity, women of childbearing age are advised to strictly avoid pregnancy during treatment with retinoids and for a further two years in case of acitretin and one month in case of isotretinoin [13].

Although our review was extensive and included searches of two databases, with inclusive search terms, our review had some limitations. Unpublished case reports were not included in our review. These may have included cases that responded unfavorably to systemic retinoids and were not reported in the literature, hence contributing to publication bias.

In our case, the patient's condition improved rapidly with acitretin after 9 years of nonresolution with corticosteroids and methotrexate. This suggests that acitretin had a real effect, although spontaneous resolution cannot be excluded. The patient's condition remained stable on 10 mg of acitretin, which she is still taking at present.

Conclusion

Our case report and literature review suggest that retinoids may be a potential treatment option for cutaneous sarcoidosis. Response to acitretin in our case was impressive. Nevertheless, further studies are needed to confirm efficacy and determine the place of retinoids, particularly acitretin, in the management of this condition.

What is new?

Sarcoidosis is a granulomatous disease that can affect multiple organ systems, including the skin. The cause of cutaneous sarcoidosis is unclear, but possibly involves a T-cell-mediated immune response to infective or environmental antigens, and/or genetic factors, which lead to activation of lymphocytes and macrophages and granuloma formation. The commonest treatment for cutaneous sarcoidosis involves topical, intralesional, and/or systemic corticosteroids. Retinoids may be a potential treatment option for cutaneous sarcoidosis; however, further studies are needed in this regard.

List of Abbreviations

TNF Tumour Necrosis Factor

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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There was no funding received for this article.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 68 years old
2	**Final diagnosis**	Cutaneous sarcoidosis responding to retinoid treatment (acitretin)
3	**Symptoms**	Erythemato-violaceous nodular infiltrates on face and ears
4	**Medications**	Corticosteroids, methotrexate, acitretin
5	**Clinical procedure**	Skin punch biopsies
6	**Specialty**	Dermatology