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Pseudorheumatoid Nodulosis of The Episclera/Conjunctiva: A New Entity.

Clinical History

A 53-year-old man presented with "bumps" noted on the inside corner of both eyes. Eight months prior to presentation he underwent a brow lift and bilateral lower eyelid repair performed in Columbia. Post operatively he developed itching, a burning sensation and erythema. When these symptoms resolved he noted "bumps" on the inner corner of eye both eyes as well as a foreign body sensation. These lesions were unresponsive to treatment with topical steroids. His ocular history was significant for a corneal foreign body in the left eye 3 years prior to presentation. His medical history included sciatica, for which he was given gabapentin, and a sleep disorder. On examination his visual acuity was 20/20 in the right eye and 20/25+1 in the left. He had normal intraocular pressures, a normal pupillary examination, full confrontation visual fields and unimpaired extraocular movements. Anterior slit lamp examination revealed meibomian gland dysfunction in both eyes with 1 mm of lagophthalmos in the left eye.

Large, circumscribed, yellow and partially immobile amorphous subconjunctival lesions that had a slightly irregular surface and were semi-confluent were observed in the nasal bulbar conjunctiva near the plica and caruncle in both eyes. A corneal scar was seen in the left eye and moderate cataracts were observed bilaterally. The fundus examination was notable for slight cup to disc asymmetry (0.35 in the right eye and 0.2 in the left) but was otherwise unremarkable. The patient was taken to the operating room for biopsy of the amorphous yellow lesions in the left eye. At surgery the lesion was adherent to the underlying sclera and two biopsies were obtained approximately one quarter of the overall lesion was removed. The conjunctival defect was closed with Tisseel fibrin glue and a subconjunctival injection of kefzol and decadron was administered.

A laboratory workup was performed including CBC, ESR, CRP, ANA, RF, ACE, lysozyme, p-ANCA, c-ANCA, quantiferon gold, bartonella henslae, RPR and a chest x ray, all of these tests were negative.

Histopathologic and Immunhistochemical Findings

Received in the pathology laboratory were 2 fragments of yellowish-tan tissue, one measuring 10 x 6 x 5 mm and the other 4 x 1 x 1 mm. Each was submitted separately and in toto for the preparation of microscopic slides. Microscopic examination disclosed in hematoxylin stained sections multiple necrobiotic foci with varying and irregular shapes and central granular and globular fragments that was faintly eosinophilic and devoid of any nuclei. In well-developed granulomas histiocytes and fibroblasts were arranged in a picket fence fashion surrounding the necrobiotic zones. Elsewhere granulomas with less regimented encircling histiocytes were seen. No histiocytic giant cells or eosinophils were identified. Scattered lymphocytes and plasma cells, also sometimes mixed together in small aggregates, were found outside the granulomas in the adjacent interstitium. The Alcian blue stain was negative in the necrobiotic foci while weakly positive in the adjacent connective tissue. The Masson trichrome stain revealed red positive staining of the globules together with faint blue staining of wisps of delicate collagen fibers in the necrobiotic foci. The periodic acid-Schiff (PAS) stain showed weak to moderate red staining of the globular and granular fragments. The elastic stain showed thin and short fragments of elastic fibers in the necrobiotic foci in comparison with the stout, elongated fibers located in the adjacent unaffected connective tissues. The Congo red stain for amyloid and the phosphotungstic acid hematoxylin (PTAH) stain for fibrin or fibrinoid material were both negative.

Immunohistochemistry confirmed CD68+ and CD163+ positivity of the palisading histiocytes. A dispersion of unorganized individual histiocytes was seen in the intervening stroma. CD3+ T lymphocytes were found preferentially situated immediately next to the histiocytic palisades but not among the palisading cells themselves. B cells were further removed from the vicinity of the histiocytic palisades than the T-lymphocytes. Small lymphoid aggregates consisted of roughly equal numbers CD3+ T lymphocytes, and CD20+ B lymphocytes, with fewer CD138 + plasma cells, which were lightly distributed in the stroma or in small lymphoid aggregates with B and T cells. CD1a+ Langerhans dendritic cells were detected in the surface non-keratinizing squamous epithelium and were also intermixed among the palisading histiocytes. No inflammatory cells were discovered in the necrobiotic foci. Antisera for the detection of IgG, IgM, IgA and IgE disclosed concentrations of the first three immunoglobulins within the necrobiotic zones but not of IgE. There was light background staining for IgG originating from blood vessels in the uninvolved.

Comments

Ocular adnexal pseudorheumatoid nodules have been most extensively analyzed by Rao and Font in a series of 21 cases that involved only the eyelids or the periorbita of the orbital rim. These lesions may be encountered in other ophthalmic sites including the epibulbar/conjunctiva.

They affect mostly younger individuals but also can occur in adults. The termed pseudorheumatoid nodules is employed because the ocular lesions typically lack an associated active arthritis or a positive rheumatoid factor. They have, however, similar histopathologic features to those of rheumatoid nodules in active disease with a positive serology. A few subtle histopathologic differences nonetheless can help to separate true from pseudorheumatoid nodules.

Whether diagnosed as true rheumatoid or pseudorheumatoid nodule, a universal common finding is that these lesions have at their centers a necrobiotic focus of acellular degenerating collagen surrounded by palisades of histiocytes and epithelioid cells. The necrobiotic collagen is often granular or globular and displays a faded eosinophilia or amphophilia in comparison with unaltered collagen. In pseudorheumatoid nodules there may also be deposition of mucopolysaccharides, which are usually absent from authentic rheumatoid nodules. Giant cells admixed with the palisading histiocytes are inconspicuous in pseudorheumatoid nodules but are more readily seen in rheumatoid examples. Fibrinoid intravascular and extravascular deposits, which can be seen in vasculitic diseases (Wegner's granulomatosis, polyarteritis nodosa, lupus erythematosus), rheumatoid arthritis has a vasculitic component can be observed in necrobiotic rheumatoid nodules but not in pseudorheumotoidal lesions. Fibrinoid material is composed of fibrin and serum-derived proteins which confer hypereosinophia and a retractile character. Neither necrohiosis of collagen nor fibrinoid deposits should be referred to as "necrosis," since this term refers to cell death and not to denaturation of non-cellular molecules with altered tinctorial properties.

The immunohistochemical studies conducted on the current patient's lesions disclosed CD168/163 + histiocytes in the palisades with a surprising number of intermixed CD1a + Langerhans cells. CD3 + lymphocytes were seen in the immediate vicinity of the palisades but not dispersed within them. CD20 + B lymphocytes and CD 138 + plasma cells were less numerous than the T cells and further removed from the palisades. Antisera against IgG, IgM and IgA demonstrated concentrations of each of these species in the necrobiotic centers, except for the deposition of IgE. Whether these concentrations of immunoglobulin are primary and integral to a local autoimmune mechanism underlying the lesions, or represent merely passive collections in the sponge-like trap of necrobiotic collagen, cannot be resolved at this time.

Single, discrete lesions or rheumatoid or pseudorheumatoid types are simply called nodules. When these form in crops, often bilaterally, they are designated as nodulosis. Rheumatoid nodulosis can be encountered in inactive disease with a long-standing quiescent period and no lingering or persistent arthritis. Rheumatoid nodulosis nonetheless manifests a positive rheumatoid factor. There is an interesting variant termed in accelerated rheumatoid nodulosis which develops after the introduction of systemic chemotherapy for active, seropositive rheumatoid arthritis.

The current case is a unique example of ocular adnexal pseudorheumatodial nodulosis, a new entity that expands the spectrum of ocular adnexal rheumatic nodules.

The biography contains papers that pertain to the lesions mentioned in the paper and are listed at the end of the Table.

The standard treatment for pseudorheumatoid nodules or nodulosis has been corticosteroids. The prognosis is outstanding regarding the absence of the later emergence of systemic rheumatoid disease and conversion to rheumatoid factor positivity.

Table: Spectrum of Clinicopathologic Features of Epibulbar Rheumaroid or Pseudorheumatoid Nodules and Nodulosis

Clinicopathologic features*	Rheumatoid nodule	Rheumatoid nodulosis	Accelerated rheumatoid nodulosis	Pseudorheumatoid nodule	Pseudorheumatoid Nodulosis
Age	49, 50, 61, 63, 72	61, 64	25 yo (in other 2 cases no age provided)	Typically in children, rare in adults	53
Sex (M,F)	4 eye lesions in F and 1 M, 1 unknown M>F in skin	2 eye lesions in F M>F in skin	1 eye lesions in M M>F in skin	Slight F>M	M
Duration of symptoms	2 months, many of unknown duration	2 months	1 month	3 weeks to 5 years	8 months
Single or multiple nodules; bilaterality	Single, multiple	multiple	Single	Single	Multiple
Pain	Irritation/pain/no pain	None	FBS	None/mild	FBS
Mobility	Mostly immobile	Mobile	Slightly mobile	Immobile	Partially immobile
Color	Yellowish/white, hyperemia, grey	Translucent/yellow tinged, hyperemia	Purulent apperance	Grey/white, hyperemia, yellow	Yellowish
Scleral thinning	Yes	Yes	No	Variable	None
Systemic disease active (A) or inactive (I) or none (N)	A	I	A to I	N	N
Rheumatoid factor positivity (+) or negativity (-)	+	+	+	-	-
Histopathology	Necrobiosis of collagen, palisading epithelioid granulomas, often fibrinoid material +/-	Lymphocytes and plasma cells, necrobiosis, palisading epithelioid granuloma, scattered giant cells, fibrinoid material +/-	Necrobiosis, palisading epithelioid granuloma, fibrinoid material +/-	Mucopolysaccharides in necrobiotic foci, palisading epithelioid granuloma, rare giant cells, no fibrinoid material.	Necrobiosis of altered collagen with mucopolysaccharides +/-, palisading fibroblasts and histiocytes, few giant cells, no fibri

					material.
Immunopathology	HLA DR + CD3+ IL-2 receptor +	ND	ND	ND	Scattered CD3+ and CD-20+ lymphocytes, CD68/163 + histiocytes and CD1a+ Langerhans cells in palisades, scattered CD138+ plasma cells, immunoglobulin deposition in necrobiotic foci (IgM, IgG, IgA not IgE).
Treatment	Observation, Intralesional steroids, Surgical excision	Steroids, intralesional injection systemic, cyclophosphamide.	Discontinue associated medications, surgical excision, hydroxychloroquine, colchicine, steroids	Excision with post-operative topical steroids	Excision
References	[11,12,14-18,35]	[5,11,20]	[11,23,24]	[1,4,7,19]	Present case

* Lesion located in the episclera and conjunctival substantia propia.

** Initially accelerated rheumatoid nodulosos was reported as an increase in the number of rheumatoid nodules (favoring the hands) in patients taking methothrexate. Subsequently, individual nodules have been reported on the episclera/conjunctiva in association with methotrexate while other cases have not specified the number of nodules present.

ND = not done.

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