ATYPICAL CASES OF SINUS HISTIOCYTOSIS (ROSAI-DORFMAN DISEASE) WITH OPHTHALMOLOGICAL MANIFESTATIONS*

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INTRODUCTION

ROSAI AND DORFMAN[1,2] GAVE THE NAME "SINUS HISTIOCYTOSIS WITH MASsive lymphadenopathy," to a disease of unknown cause observed mainly in children who had presented clinically with manifestations suggestive of Hodgkin's disease or other malignant lymphomas. We have made the histopathologic diagnosis of sinus histiocytosis in two cases that had some very atypical features. Neither patient had significant lymphadenopathy and in neither case was sinus histiocytosis considered clinically.

CASE REPORTS

CASE 1

A 70-year-old black man from Winchester, Virginia, had multiple, very firm masses in the upper and lower eyelids of both eyes for about 3 years (Fig 1). They had the consistency of a rubber eraser. He had also complained of hoarseness and weight loss. In September 1984, long before he was referred to the Center for Sight at Georgetown University, he had already had biopsies of his laryngeal and palpebral lesions. The former had originally been interpreted as suspicious but not diagnostic of a small cell tumor, and the latter as a chalazion; and on subsequent review at the

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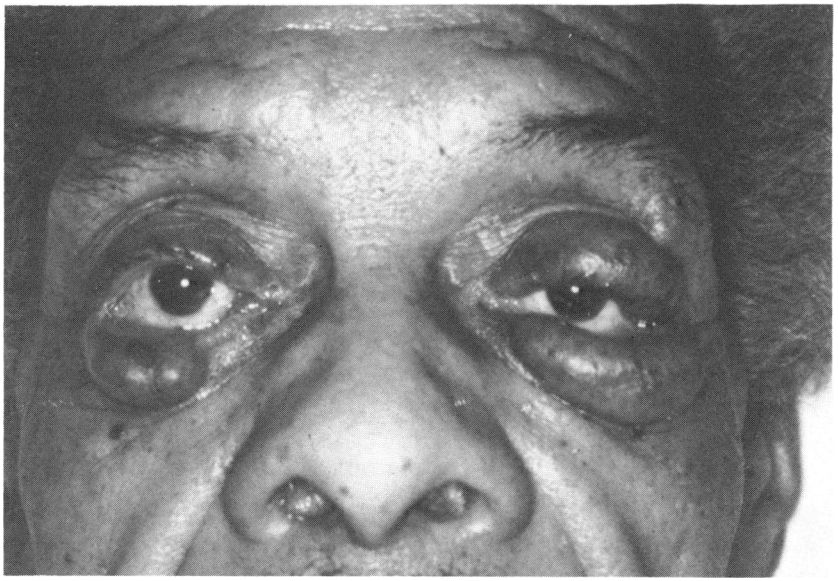


FIGURE 1
Multiple firm subcutaneous masses are present in eyelids of both eyes. AFIP Neg No 88-6876.

Armed Forces Institute of Pathology (AFIP), both lesions were considered atypical lymphoplasmacytic infiltrates. In January 1986, additional biopsies were obtained from the right and left eyelids, and at that time the local pathologist rendered a histologic diagnosis of "eruptive xanthomas." The senior author who was then asked to review the case, was impressed by the similarity of the inflammatory reaction to that which is typical of sinus histiocytosis of Rosai and Dorfman,[1,2] but there were also histologic features suggestive of rhinoscleroma. The history at that time also indicated that the patient had nasal involvement, which provided another reason for considering rhinoscleroma. Gram stains and Warthin-Starry silver stains were therefore prepared in an effort to demonstrate *Klebsiella* rhinoscleromatis, and additional special stains for acid-fast bacteria and fungi were also examined, but no infectious agents were demonstrated. The case was then evaluated at the AFIP in the Departments of ENT Pathology and Infectious Diseases where it was the consensus of reviewers that no microorganisms were present and that the histologic features were not typical of rhinoscleroma. Consultants at the AFIP and others including Drs Rosai, Dorfman, Hartsock, and Font all concurred in the histologic diagnosis of sinus histiocytosis. The patient was then referred to the Center for Sight, Georgetown University Medical Center, for oculoplastic surgery and further studies.

Histologically the several specimens from the eyelids (Fig 2) and that from the larynx (Fig 3) each revealed a massive proliferation of histiocytes containing

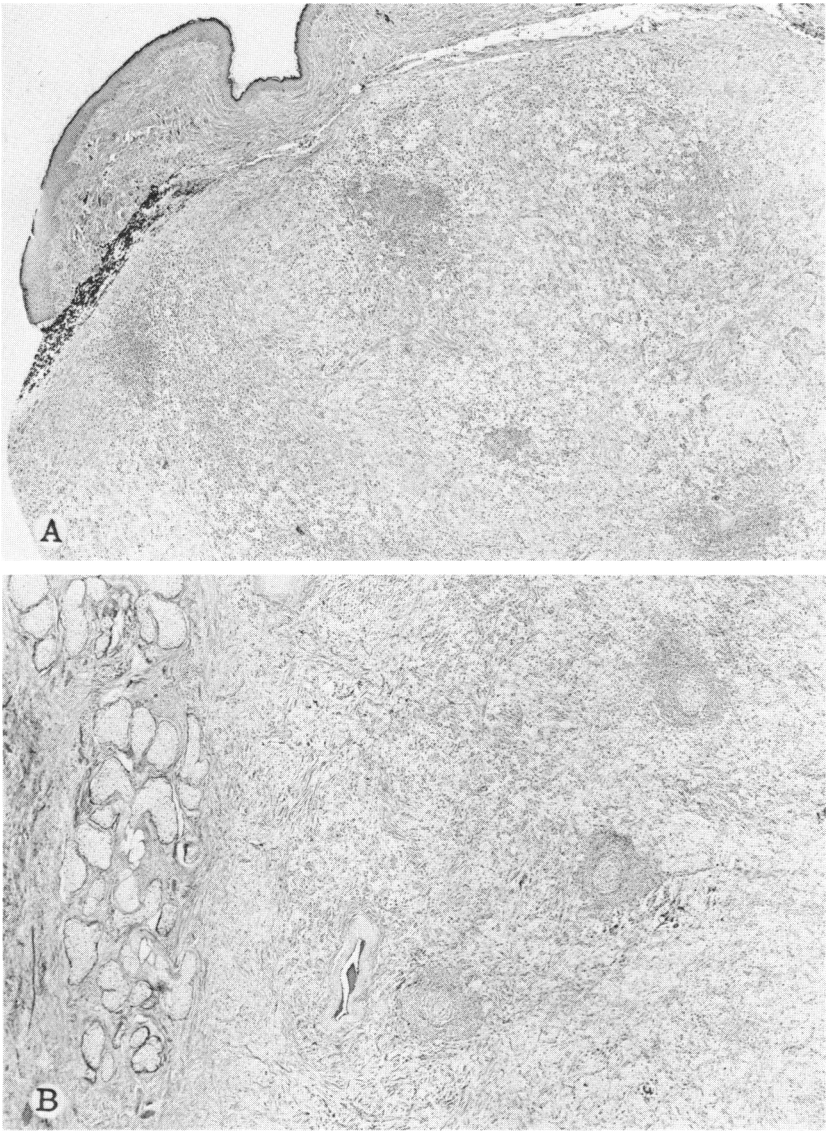


FIGURE 2

A: Subcutaneous masses are composed predominantly of large, pale-staining histiocytic cells, interspersed with a light diffuse lymphoplasmacytic infiltrate, and focal aggregates of lymphocytes (H&E, × 30) AFIP Neg No 88-6877. B: Deep margin of one of the palpebral masses abuts against the tarsal plate with its meibomian glands, shown along left margin of field. In this field, three of the lymphocytic aggregates are follicles with conspicuous germinal centers (H&E, × 30) AFIP Neg No 88-6878.

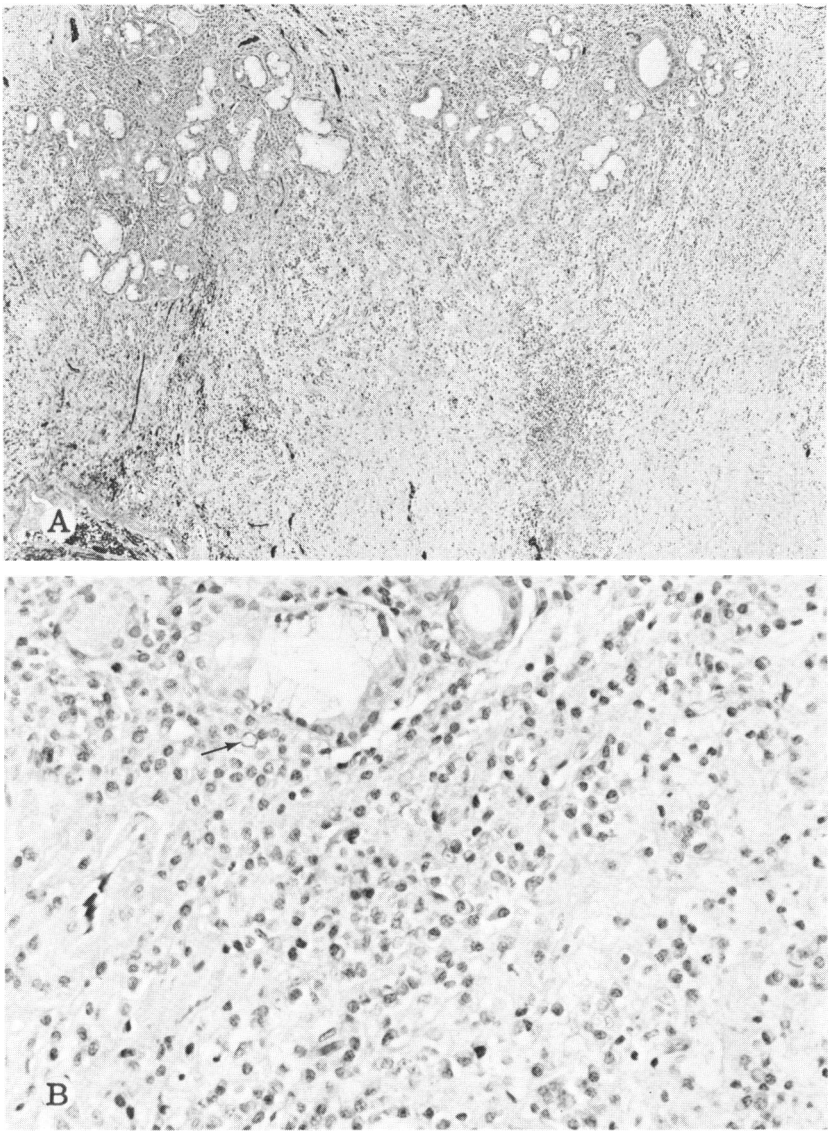


FIGURE 3

A: Submucosal lesion excised from larynx reveals a histiocytic and lymphoplasmacytic infiltrate. Mucus-secreting submucosal glands are present in the upper half of the field. The large pale-staining areas shown in the lower half of the field are areas in which histiocytic infiltration is pronounced (H&E, × 50) AFIP Neg No 88-6879. B: An infiltrate of lymphocytes and plasma cells is present among the histiocytes. The *arrow* indicates a Dutcher body (H&E, × 30) AFIP Neg No 88-6880.

abundant very pale-staining vacuolated cytoplasm and an admixture of plasma cells and lymphocytes (Figs 4 and 5). While the latter were often aggregated in nodular collections, or less often, follicles with germinal centers (Fig 2B), the former were more diffusely present and associated with Russell bodies (Figs 4B and 5B), or less frequently, Dutcher bodies (Fig 3B). A conspicuous feature that is highly characteristic of sinus histiocytosis was the presence of intact lymphocytes and plasma cells within the cytoplasm of many of the histiocytes (Figs 4 and 5). The cytoplasm of the histiocytes generally gave a strongly positive immunoperoxidase staining reaction for S-100 protein (Fig 6). In such preparations, the presence of lymphocytes or plasma cells within the cytoplasm of histiocytes could be demonstrated very vividly as the lymphoid cells, which were stained only by the counterstain, were surrounded by the brown-staining cytoplasm of the histiocytes. Immunoperoxidase preparations revealed either weakly positive or negative staining for lysozyme. With frozen sections stained with Oil red O, only occasional histiocytes were demonstrated to contain lipid droplets. Formalin-fixed and paraffin embedded tissues reprocessed for electron microscopy revealed the histiocytes to have oval nuclei with fine, evenly distributed chromatin and eccentric nuclei (Fig 7). The lucent cytoplasm of these histiocytes contained many small mitochondria, cytoplasmic vacuoles, and phagosomes. Intact and disintegrated lymphocytes and plasma cells were present within the cytoplasm of these cells. A few profiles of endoplasmic reticulum were seen (Fig 8). Birbeck granules were not observed. Rounded, electron-dense Russell bodies were noted. A few electron dense crystalloid structures without internal periodicity were seen inside large plasma cells (Fig 9), probably representing elongated forms of Russell bodies.

CASE 2

An otherwise healthy 13-month-old white boy was referred to the Center for Sight for evaluation of an enlarging lesion involving the left eye. On examination by the referring ophthalmologist 2 months earlier, an elevated, fleshy and well circumscribed epibulbar tumor was noted, lying just posterior to the limbus at 12 o'clock. At the time of our examination, the lesion measured 8 mm vertically by 6 mm horizontally with 3 mm of superficial corneal invasion (Fig 10). The remainder of the examination revealed no abnormalities in either eye or ocular adnexa.

The results of clinical laboratory studies were: a white blood cell count of 9,000 cells/mm^3 with a normal differential, a hematocrit of 38%, a Westergren erythrocyte sedimentation rate of 5 mm/hour, and a negative chest x-ray. A complete physical examination revealed only minimal inguinal lymphadenopathy, which was not considered to be clinically significant.

Complete surgical excision of the mass was performed by superficial sclerokeratectomy under general anesthesia. After 2 years there has been no evidence of local recurrence or of systemic disease.

Microscopic examination of the excised corneoscleral and conjunctival tissue revealed a non-encapsulated inflammatory lesion consisting predominantly of large ill-defined aggregates of histiocytes with an admixture of lymphocytes and plasma

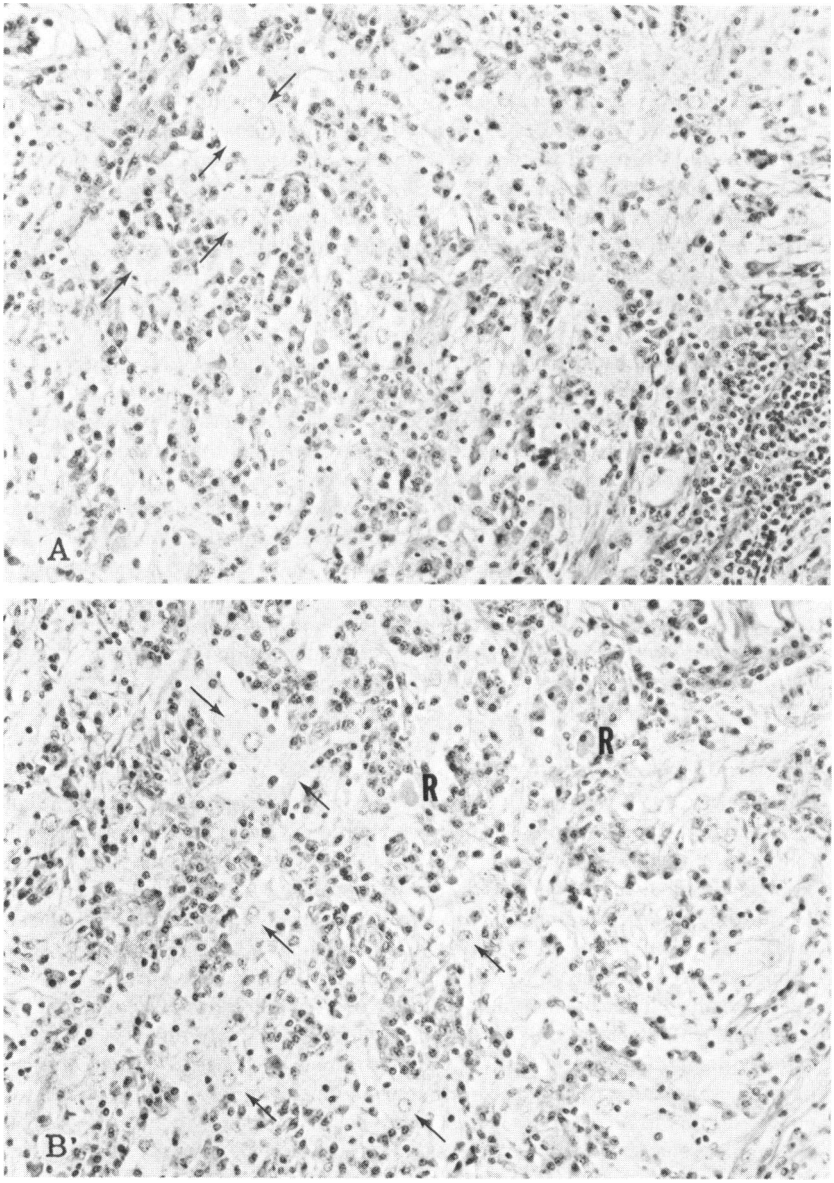


FIGURE 4

A&B: Subcutaneous lesion of eyelid; the large cells with abundant pale-staining cytoplasm indicated by *arrows* are histiocytes, while the small, dark cells are lymphocytes and plasma cells, many of which are within the cytoplasm of the histiocytes. Two Russell bodies are indicated by R (H&E, × 200) AFIP Neg Nos 88-6881 and 88-6882, respectively.

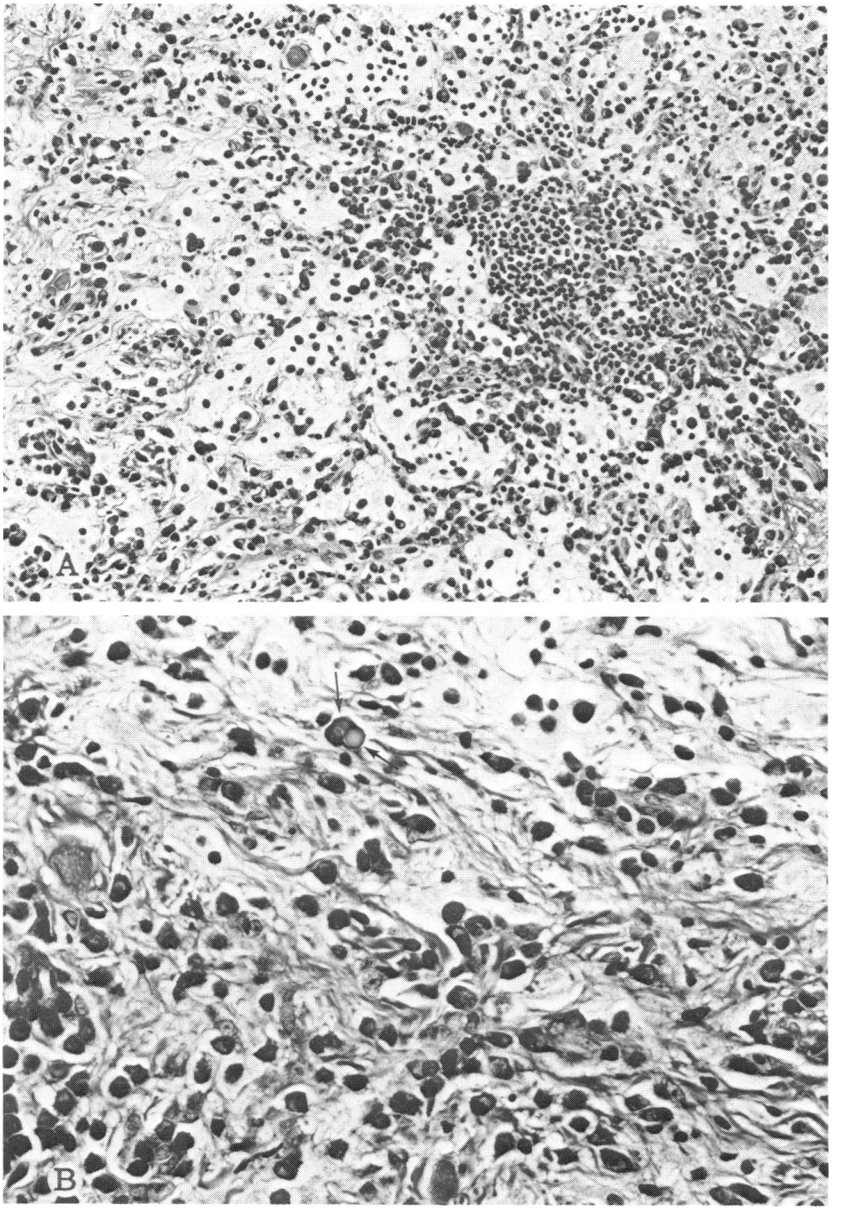
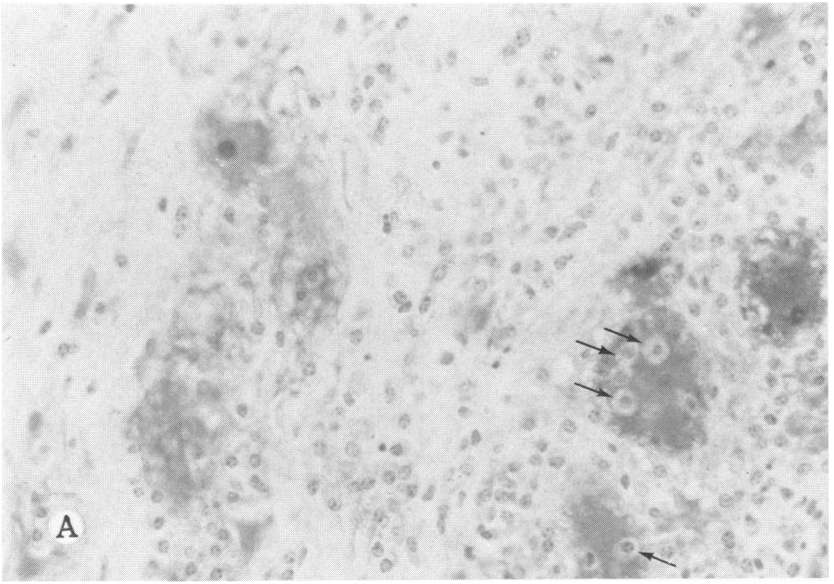


FIGURE 5

A&B: Fields of lid lesion in which intracytoplasmic presence of lymphoiud cells is especially conspicuous. *Arrows* indicate a Russell body (A: H&E, × 200, AFIP Neg No 87-6307; B: H&E, × 400, AFIP Neg No 87-6300).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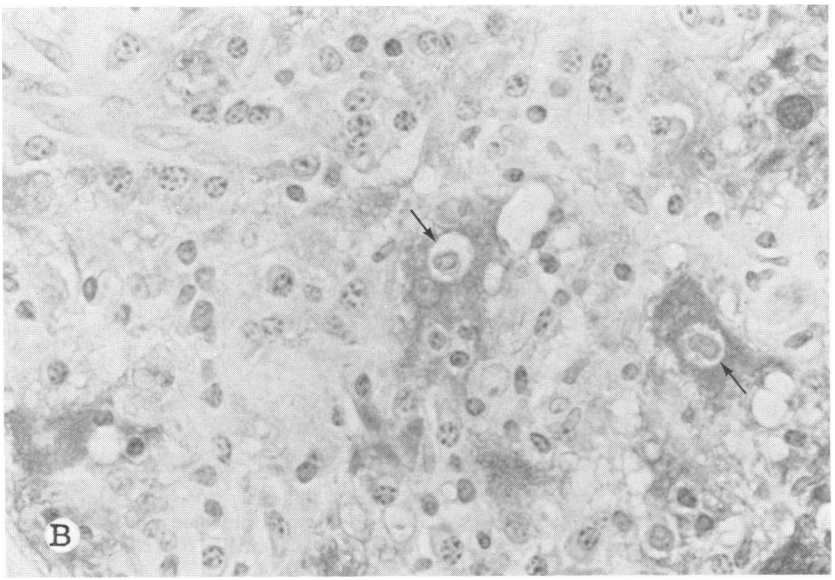
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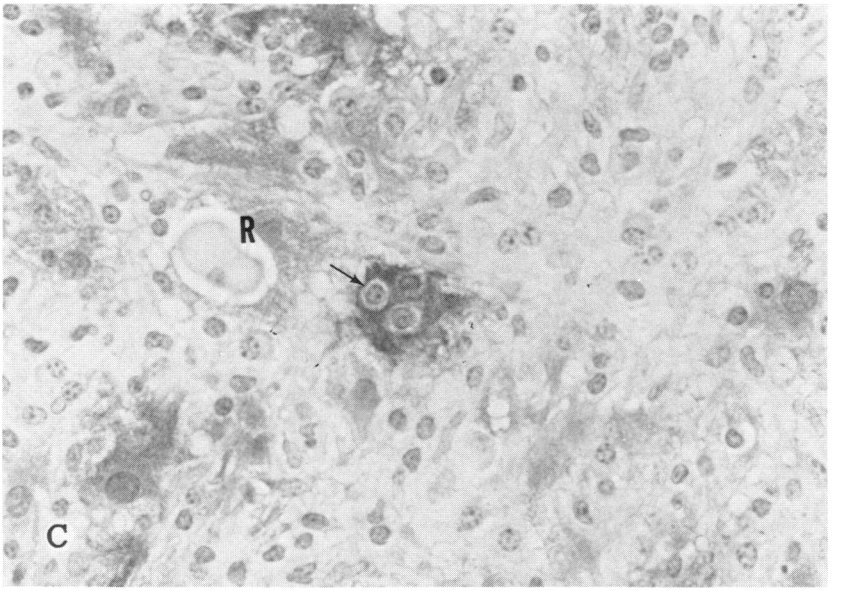

FIGURE 6
A, B, & C: Lid lesion: large cells with abundant deeply-stained cytoplasm are histiocytes exhibiting positive staining for S-100 protein. *Arrows* indicate unstained lymphoid cells that are outlined by the deeply-stained cytoplasm. A Russell body is indicated by R (immunoperoxidase stain for S-100 protein, × 400). AFIP Neg Nos 88-6884, 88-6885, and 88-6883, respectively.

cells (Fig 11). The histiocytes were characteristically large cells with abundant pale-staining and finely vacuolated cytoplasm. They had large, vesicular round nuclei that contained prominent nucleoli. Plasma cells and lymphocytes were seen in smaller numbers, some of which were within the cytoplasm of the histiocytes (Figs 12 and 13). Neutrophils were present but not conspicuous. Immunocytologic staining performed on tissue sections revealed positive staining for S-100 protein in the cytopolasm of most of the histiocytes (Fig 14), and minimal or absent staining for lysozyme.

DISCUSSION

Although cases of sinus histiocytosis with massive lymphadenopathy had already been reported by Destombes[3] and by Azoury and Reed,[4] it was not until 1969, with its description by Rosai and Dorfman, that sinus histiocytosis with massive lymphadenopathy became a well-recognized clinicopathologic entity.[1] The cases collected by Rosai and Dorfman[1,2] featured painless enlargement of cervical and other lymph nodes, but many descriptions of

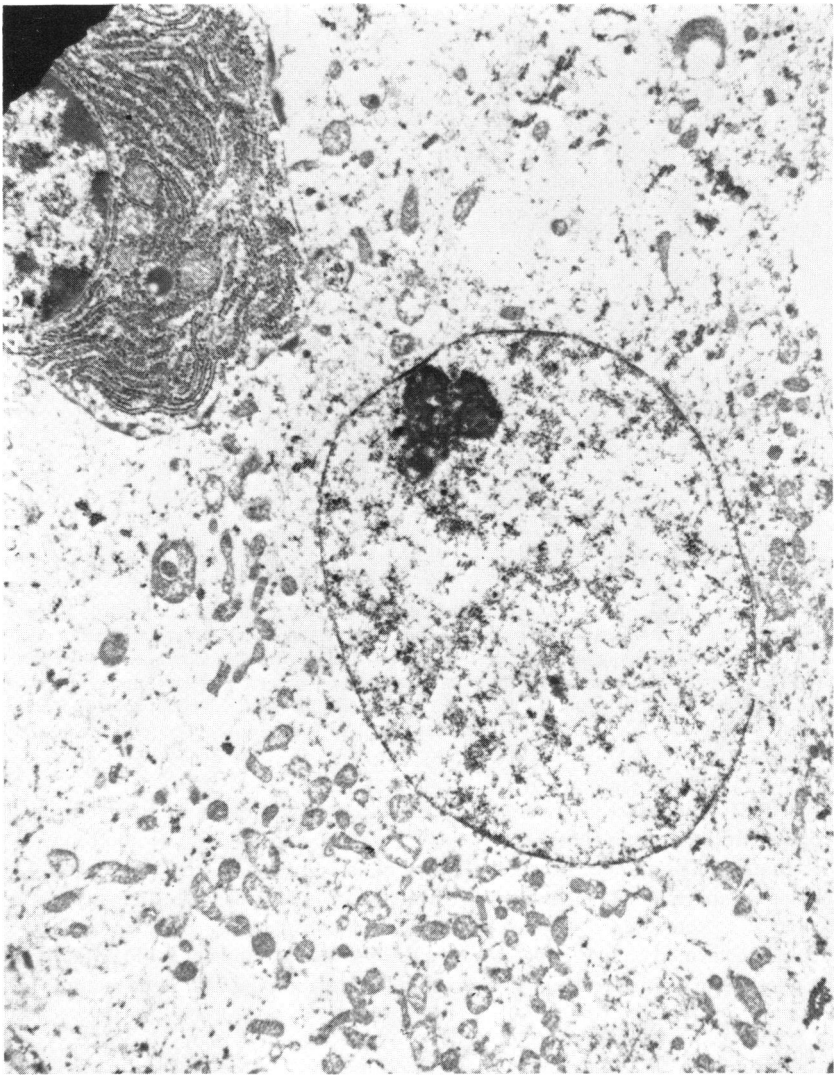

FIGURE 7
Electron micrograph of lid lesion showing a large histiocyte with an oval nucleus containing an eccentric nucleolus and fine, evenly distributed chromatin. The lucent cytoplasm contains many small mitochondria. An intact plasma cell contained within the histiocyte is seen in the left upper corner (× 8400).

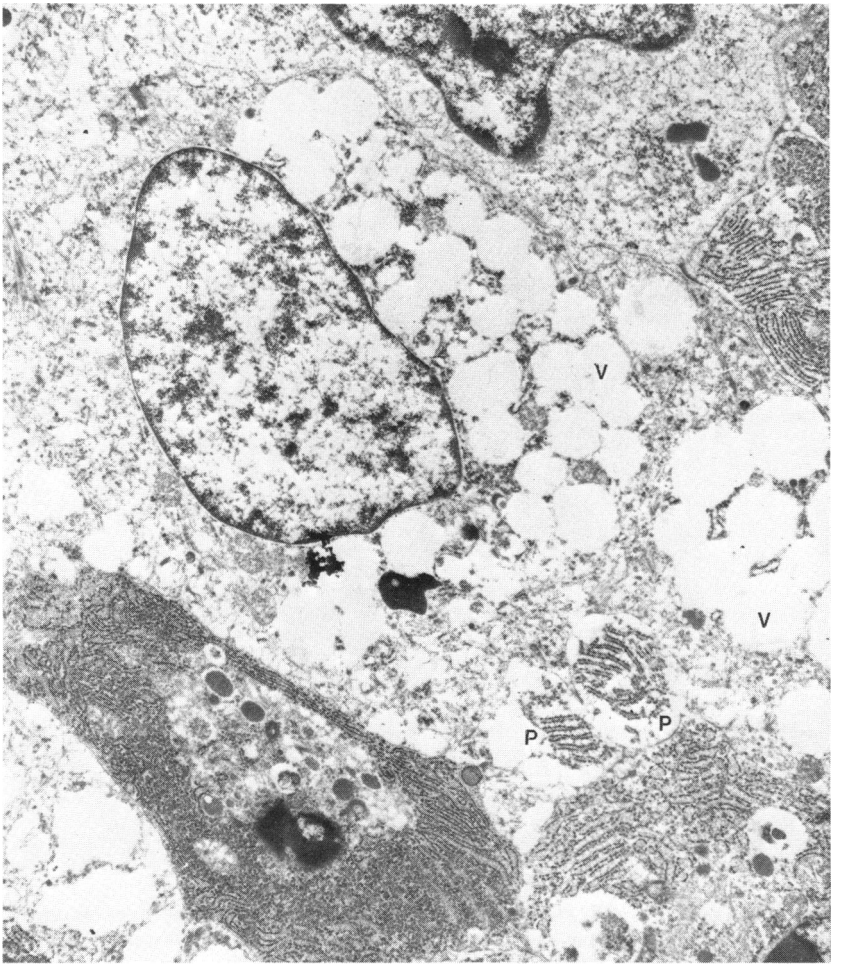

FIGURE 8
Many vacuoles (V) are present within the cytoplasm of a histiocyte. In the right lower corner, a portion of a plasma cell is present near two phagosomes (P) of the histiocyte. These phagosomes contain profiles of rough surfaced endoplasmic reticulum, apparently pinched off from the plasma cells. In the left lower corner, there is a portion of another plasma cell engulfed by the histiocyte (× 8400).

extranodal involvement as well as fever, leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia, and other serological abnormalities have been published.[2-17]

Ophthalmic manifestations most often have been characterized by masses in the eyelids or orbital soft tissues.[2,3,5,6,8,12] Involvement of the eyeball

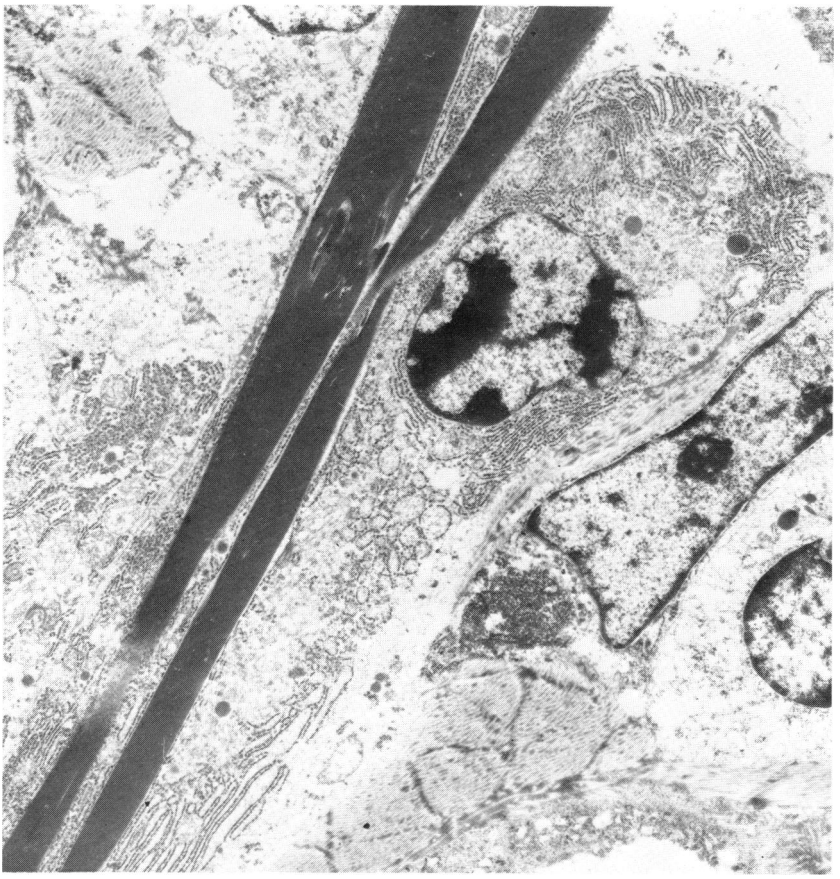

FIGURE 9
Within a large plasma cell, electron-dense homogeneous crystalloid structures are seen. Higher magnification did not show internal periodicity. These structures may represent elongated forms of Russell bodies (× 8400).

itself is rare with only two such cases appearing in the literature. In one report, a patient with systemic sinus histiocytosis developed a unilateral panuveitis,[12] while in the other, a patient with systemic sinus histiocytosis developed a unilateral anterior uveitis which responded to therapy for her systemic disease.[15] Neither of these two patients was reported to have had involvement of other ocular adnexa. Ophthalmologic manifestations of sinus histiocytosis may be the initial or the only expression of the disease.[8,12] They were described in 13 patients in a series of 113 cases,[12] with lesions of the eyelid and orbital masses being the most frequent. Orbital or

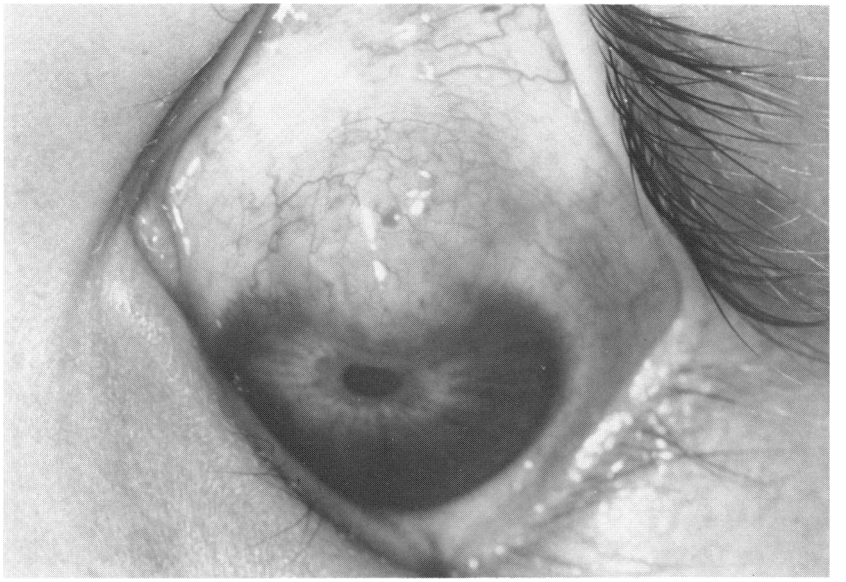

FIGURE 10
Hyperemic epibulbar lesion with intracorneal extension in a 13-month-old boy. AFIP Neg No 88-6970.

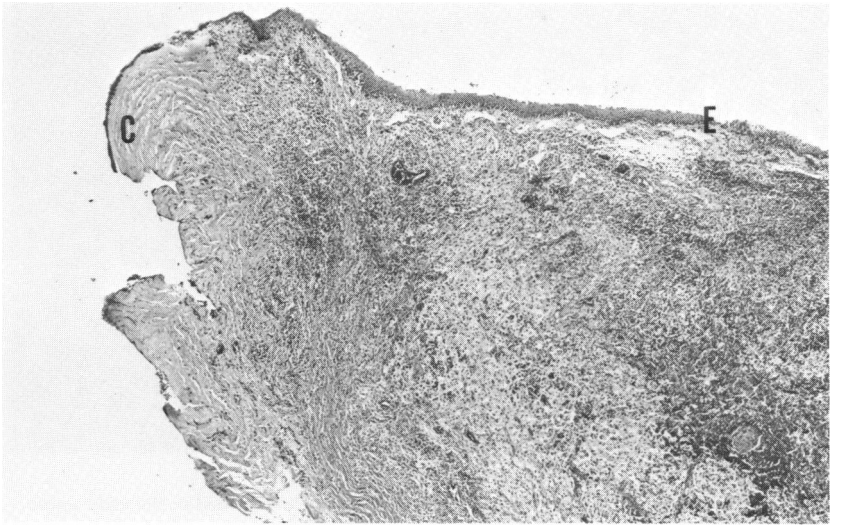

FIGURE 11
Excised corneoscleral lesion shown in Fig 10 is an inflammatory infiltrate composed of large pale-staining histiocytes and more deeply stains lymphocytes and plasma cells. (C), Cornea; (E), epithelium of conjunctiva (H&E, × 40) AFIP Neg No 87-6316.

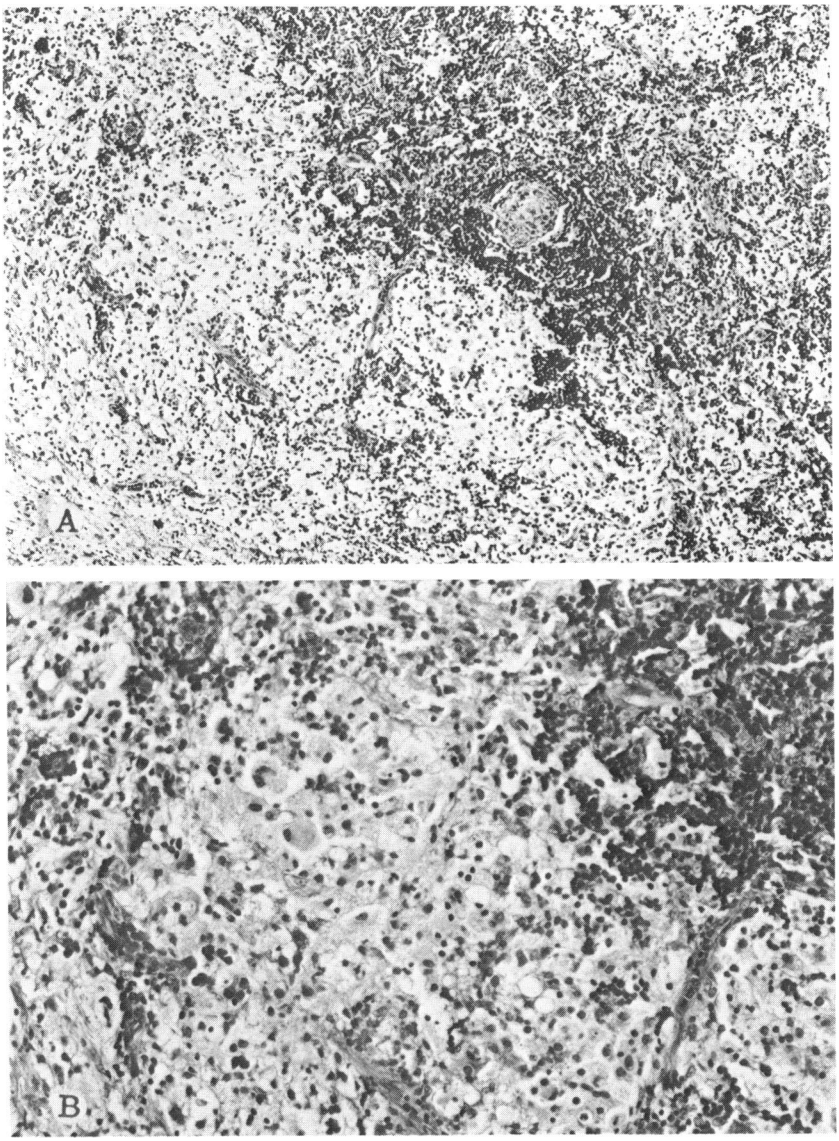

FIGURE 12

A: The pale-staining areas occupying the left lower half of the field and in the right upper corner are where large histiocytic cells predominate while in the center of the field there is a lymphocytic nodule with a small germinal center (H&E, × 100) AFIP Neg No 87-6317. B: A light but diffuse infiltrate of lymphocytes and plasma cells is present among the large pale-staining histiocytes. Many of the lymphoid cells are within the cytoplasm of the histiocytes (H&E, × 200) AFIP Neg No 87-6319.

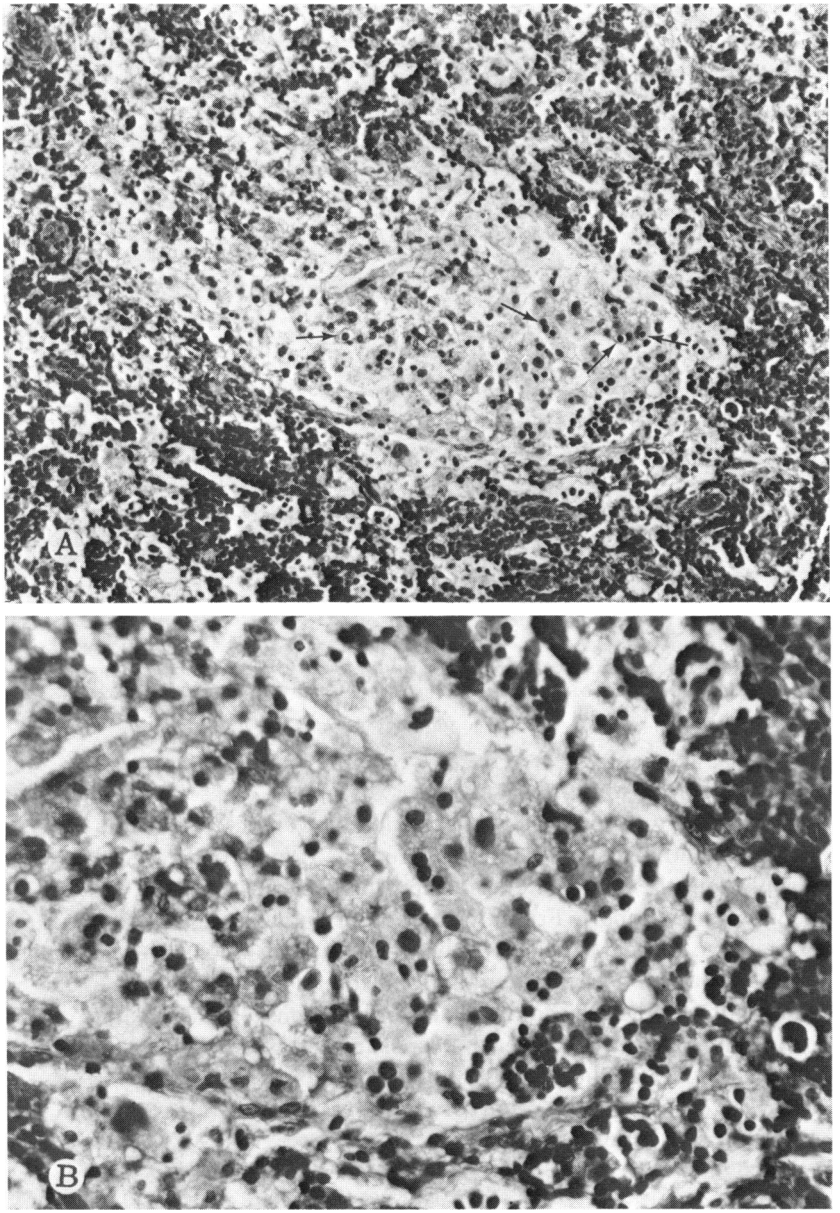

FIGURE 13

A: *Arrows* indicate lymphoid cells within the cytoplasm of histiocytes (H&E, × 200) AFIP Neg No 87-6320. B: Enlargement of central part of field shown in A (H&E, × 400) AFIP Neg No 87-6321.

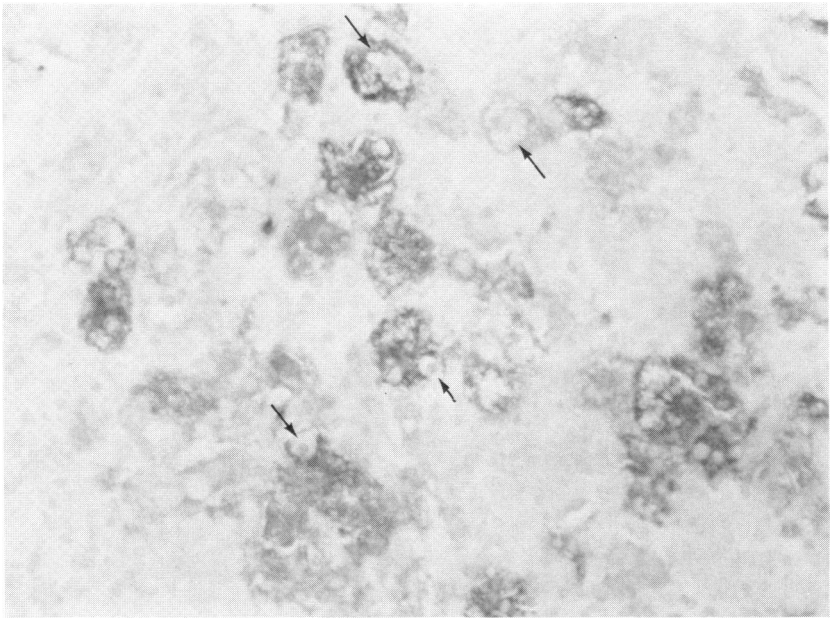

FIGURE 14
The large dark cells are histiocytes stained for S-100 protein in which unstained lymphoid cells may be seen (*arrow*) (immunoperoxidase, × 400) AFIP Neg No 88-6024.

lid involvement was the first sign of disease in 6 cases, while 6 other patients went on to develop orbital or lid involvement from 6 months to 20 years after other tissues had been affected. In only one case was orbital involvement the only evidence of sinus histiocytosis.

In an earlier report, Friendly et al[8] described four other cases in which orbital involvement was among the initial manifestations. In one of their cases, ipsilateral corneal ulceration led to endophthalmitis necessitating enucleation. Although conjunctival manifestations (eg, injection, dry eyes, recurrent conjunctivitis, etc) and exposure keratitis secondary to marked proptosis with inability to close the lids have been described,[2,8,12] we are not aware of any previous report of a solitary corneoscleral lesion such as we have described in our second case.

What makes our first case so very atypical is the patient's age (68 years) at initial presentation. We were unaware of any reports in patients older than he. Because of this and also because several pathologists, who had studied the tissues excised from the larynx and eyelids before the case was submitted in consultation to the senior author, had failed to make or even

suggest the correct diagnosis, sections were sent in consultation to both Drs Rosai and Dorfman, and each was informed of the patient's age and of the lack of lymphadenopathy. Despite these unusual features neither consultant had any hesitancy in confirming the histologic diagnosis of sinus histiocytosis. Dr Dorfman[18] commented, "We have now encountered a significant number of adult patients with extranodal manifestations and there appears to be an unusual prediletion for soft tissues around the eye and orbit." Dr Rosai[19] stated, "In our experience, which now covers approximately 320 cases of this entity, we have seen extranodal manifestations in about one-quarter. The upper respiratory tract and the stomach region are among the most common. In some cases, like your patient, the extranodal manifestations are the dominant feature of the disease, the lymphadenopathy being minimal or absent. Although most patients with this disease are children or adolescents, we have seen it in all age groups including octogenarians." The results of our electron microscopic studies in case 1 were similar to those described in previous reports[20,21] including one in which both Drs Rosai and Dorfman were co-authors.[20]

These cases underscore two criticisms of the original name given by Rosai and Dorfman. First, significant lymphadenopathy is not an essential feature of the disease. The second is conceptual, in relation to the lineage of the histiocytes, which Rosai and Dorfman believed to have been derived from those found in the peripheral sinuses of lymph nodes. It doesn't seem reasonable to continue to believe in such a histogenesis in view of the many extranodal lesions observed in the absence of lymph node enlargement. Dorfman agrees, and he commented that the literature is increasingly using the eponym "Rosai-Dorfman" disease.[18]

Rosai and Dorfman, however, may have been correct in suggesting that the histiocytes in this disease are different from those in other histiocytic disorders. There are several distinctive histiocytic lesions that may involve the eyelids, conjunctiva, orbit, and/or the eye itself, including juvenile xanthogranuloma,[22-25] histiocytosis X (especially eosinophilic granuloma and Hand-Schuller-Christian disease),[24-27] xanthelasma and other xanthomatous conditions including Erdheim-Chester disease,[25,28] necrobiotic xanthogranuloma,[25,29,30] fibrous histiocytoma,[31,32] and other related conditions.[25] With the exception of histiocytosis X, the histiocytes in these entities do not characteristically exhibit positive staining for S-100 protein, but they do stain for lysozyme.[33-35] In histiocytosis X, the histiocytes have been characterized as having a distinctive cytoplasmic organelle, the Birbeck granule, which along with positive staining for S-100 protein is also a feature of the Langerhans cells of the epidermis and conjunctival epithelium. In sinus histiocytosis, however, Birbeck granules have not been

found,[20,21] although the histiocytes do stain for S-100 protein.[33,34] Dr Elner, a former Fellow at the AFIP, in collaboration with Drs Langloss and Hidayat studied six ophthalmic lesions, not including the two cases we are reporting, and in all six cases, most of the large histiocytes contained S-100 protein but not lysozyme.[33] Thus it appears that in this curious condition the histiocytes belong to a class that is poorly phagocytic, lack or contain only small amounts of lysozyme, contain S-100 protein, and are antigen-presenting.[33] Generally included in this group are the Langerhans cells of the epidermis, veiled histiocytes, and interdigitating reticulum cells, probably including those that reside in the peripheral sinuses of lymph nodes.[33,34]

One final comment about the rarity of the limbal lesion in case 2 is appropriate. We have already pointed out that we have not found any reports of a similar lesion in the literature on sinus histiocytosis. From the perspective of epibulbar tumors in children, any histiocytic mass is also rare. Elsas and Green[36] reported on 302 cases in which the lesion was excised and examined microscopically. A single fibrous histiocytoma was the only histiocytic lesion in that large series. More recently Cunha et al[37] reviewed the Wills Eye Hospital experience with 282 biopsied epibulbar tumors in children; no mention was made of any histiocytic lesions.

SUMMARY

Sinus histiocytosis with massive lymphadenopathy is a non-neoplastic disease of unknown cause observed mainly in children with markedly enlarged cervical or other lymph nodes. We have reported two very atypical cases with extranodal manifestations that required ophthalmological consultation. Neither patient had significant lymphadenopathy. One patient, who had tumors of all four eyelids as well as lesions of the nose and larynx, was 68 years old when first examined, and 70 at the time of his last surgical procedure. The other patient, a 13-month-old child, had a unique corneoscleral lesion as his only clinical manifestation. The excised tissues obtained from the eyelids and larynx in case 1 and from the corneoscleral lesion in case 2 revealed characteristic histopathologic features of sinus histiocytosis (Rosai-Dorfman disease), including strongly positive immunoperoxidase staining for S-100 protein in the cytoplasm of most of the histiocytes.

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DISCUSSION

DR FREDERICK A. JAKOBIEC. Doctor Zimmerman and his co-authors have amplified the ophthalmologic manifestations of a disease that had not been well characterized until about 20 years ago, but a disease which now has been recognized to have important ophthalmic expressions, even in the absence of significant involvement elsewhere in the body. Around 10% of patients with this disease can be expected to have a current or future ocular adnexal involvement (lids, conjunctiva, and orbit, but hardly ever intraocular). Most of the ophthalmic lesions are managed by local resection. It appears that corticosteroid therapy, chemotherapy, and radiation therapy are not particularly advantageous for local or systemic disease, and in fact can precipitate a fatal outcome. Many untreated cases of systemic sinus histiocytosis spontaneously regress; unfortunately, patients are at a greater risk for early fatality than an age-matched population.

In a group of 215 patients with this disease, there were 14 known fatalities, with an average age at death of 33 years (Foucar et al, *Cancer* 1984; 54:1834). Two patients died from the effects of locally infiltrative lesions involving a vital organ, while four others had advanced multifocal disease at autopsy. In five patients, death waas the result of defined immunologic abnormalities, and three deaths were the consequences of infections. There is a wide range of immunologic abnormalities that can accompany this disease, including autoimmune joint disese, Coombs-positive anemia, systemic amyloidosis, Wiskott-Aldrich syndrome, immunologic pancytopenia, asthma, glomerulonephritis, the nephrotic syndrome, and anti-factor VIII antibodies. To date there is no evidence that either a malignant histiocytic tumor or a malignant lymphoma can evolve out of sinus histiocytosis, as has been demonstrated in multicentric Castleman's disease, angioimmunoblastic lymphadenopathy, and the inflammatory infiltrates of Sjögren's syndrome (malignant lymphoepithelial lesion).

I would now like to discuss some aspects of the histogenesis of this entity, particularly against the background of the recent explosion of information about "histiocytes" (Chestnut et al, *CRC Crit Rev Immunol* 1985; 5:263, Poulter et al, *Scand J Immunol* 1985; 21:401, Franklin et al, *Lab Invest* 1986; 43:322, Betancourt et al, *J Immunol* 1987; 139:3725, and Radzun et al, *J Leuk Biol* 1988; 43:41).

If the 1970s were the decade of the lymphocyte, I believe that the 1980s have been the decade of the "histiocyte" and its congeners. Headington has written a stylistically colorful and scientifically sarcastic editorial (*Arch Dermatol* 1986; 122:532) entitled "The Histiocyte: In Memoriam." He states: "Reports of the demise of the *histiocyte* (italics to emphasize my [the authors's] disfavor) could not be too greatly exaggerated. Yet, the term perniciously remains as a curious and even arcane anachromism. . . . The term histiocyte may be used in almost any context regardless of its ancestry or cell lineage . . . somatocyte would be just as specific." It is my own impression that while the obsequies for the histiocyte or reticulum cell may be underway, these sobriquets are not about to disappear and will continue to decorate many scientific articles and to designate many clinicopathologic entities. For this reason, I am not going to tilt against the terms as such, but I would like to point out how there has developed a major division in the nosology of what used to be collectively termed macrophages, reticulum cells or histiocytes, much like the functional dichotomy that now exists between B- and T-lymphocytes (the former synthesizing antibodies, and the latter responsible for cell-mediated immunity).

It is now understood that histiocytes/monocytes can be divided into two major compartments: one that is constituted by phagoytic cellular populations, and the other by dendritic cells which are considered to be immune-accessory or antigen-processing and presenting cells. These organizational principles supersede what was once called the reticuloendothelial system. Both compartments are believed to derive ontogenetically from the progeny of bone marrow stem cells. It is easy enough to conceptualize the phagocytic compartment; these are the mononuclear cells that ingest organisms, extracellular material (lipid in xanthoma cells, melanin in melanophages, etc), and they are endowed with cytoplasmic enzymes (eg, lysozyme, acid phosphatase, and alpha-1-antichymotrypsin) to subserve these functions. Such cells are scattered in the liver, lung, synovium, spleen, lymph nodes, and at all sites of active inflammation. One might regard them as the proletarians of the monocytic system. Far more refined and aristocratic are the various species of dendritic cells, which are not actively phagocytic; they are so-termed because they extend long cellular processes which are the sites for antigen or immune-complex adsorption. Electron microscopy reveals their dendritic shape, intercellular desmosomes (visible by light microscopy with antibodies against desmoplakin), the absence of phagocytosed cytoplasmic debris, and small collections of electron-dense granules next to one pole of the nucleus. Dendritic cells can internalize antigen, process it, re-express it on their membrane surface, and present it to either B- or T-lymphocytes in the context of major histocompatibility complex class II antigens (Ia or HLA-DR molecules). The latter are in a certain sense receptors that can associate peptide antigens directly with them. There is a spate of monoclonal antibodies, too numerous and abstruse to list here,

which can distinguish between the phagocytic and the dendritic compartments of the monocytic system. The main types of dendritic cells which have been discovered to-date are: Langerhans cells, follicular dendritic (reticulum) cells, interdigitating dendritic (reticulum) cells, veiled cells, and indeterminate cells. Monoclonal antibody and histochemical studies disclose heterogeneous staining properties within and between these classes of cells, probably bespeaking disparate functional and activational states. The overarching functional purpose of dendritic cells is to form networks that organize immunologic microenvironments for immunocytes (ie, B- and T-lymphocytes).

The Langerhans cell resides in the epidermis and within the conjunctival epithelium (Sacks et al, *Ophthalmology* 1986; 93:1089 and *Ophthalmology* 1986; 93:1276), but may also be found in various parenchymal organs including the lacrimal gland (Wieczorek et al, *Ophthalmology* 1988; 95:100) and even in the dermis, the substantia propria of the conjunctiva, and in lymph nodes during their peripatetic migrations. These cells are S-100 positive and OKT6 positive, and display the Birbeck granule by electron microscopy; they interact with T-lymphocytes. The follicular center dendritic cells are present in lymphatic germinal centers and process antigen for presentation to B-lymphocytes (Carbone et al, *Hum Pathol* 1988; 19:51, Ratech et al, *Hum Pathol* 1988; 19:89). The AIDS virus can infect and kill these cells, leading to further deregulation of B-lymphocytes and lymphadenopathy (Piris et al, *Am J Clin Pathol* 1987; 87:716). the interdigitating dendritic cells are present among T-lymphocytes in the paracortical regions of lymphoid tissue. the interdigitating dendritic cells are usually S-100 positive and OKT6 negative, similar to the immunophenotypic features of the cells in sinus histiocytosis (Miettinen et al, *Am J Clin Pathol* 1987; 88:270-277). Veiled cells (a description that is due to their distinctive processes) comprise 30% of the cells in lymph draining from the skin and can recirculate through the bloodstream; they can be any of the foregoing types, and are believed to be able to carry processed antigen to lymph nodes for further presentation to lymphocytes and can also serve as long-term memory cells themselves. On the other hand, indeterminate cells are any type of the foregoing dendritic cells found in tissue during their migratory phases. Dendritic cells are prominent in autoimmune diseases: for example, in ocular cicatricial pemphigoid, they are 25-fold increased over uninflamed control tissues (Wieczorek et al, *Invest Ophthalmol Vis Sci* (Suppl) 1988; 29:321).

Nobody knows quite precisely which monocyte or dendritic cell is responsible for the proliferation in sinus histiocytosis, whereas it is quite clear that the Langerhans cell is responsible for the lesions that we diagnose as histiocytosis-X. My own suggestion would be that the T-zone interdigitating dendritic cell is an excellent candidate, particularly since this is not a phagocytic cell; the cells in sinus histiocytosis are not phagocytic or even enzymatically related to phagocytes (they are negative for lysozyme and alpha-1-antichymotrypsin). The presence of lymphocytes in the cytoplasm of the histiocytes of sinus histiocytosis has been interpreted by some investigators to indicate a phagocytic process, but these lymphocytes actually tunnel into the cytoplasm (emperipolesis—similar to sticking one's finger into an inflated balloon). There is no evidence of apoptosis of the lymphocytes, nor

are there any lymphocytic degradation products in the cytoplasm of the histiocytes. Furthermore, the emperipoletic lymphocytes typically are immunophenotypically of the helper/inducer subset (Bonetti et al, *Virchows Arch a* 1987; 411:129-135), providing further evidence for a possible relationship to interdigitating dendritic cells. The one morphologic aspect of these lesions which does not quite fit with this hypothesis, however, is the early localization within lymph nodes of the proliferating cells to the sinus regions, which are populated by cells that are believed to belong to the phagocytic arm of the monocytic system. a counter to this awkward anatomic feature is that the cells are merely trapped in the sinuses rather than having originated there. Don't forget that this is a systemic disease, and the cells traverse many nodal and extranodal sites including the ocular adnexa. The fact that the cells in sinus histiocytosis are not dendritic in shape is not especially problematic; those in histiocytosis-X deriving from the dendritic Langerhans cell also exhibit a polygonal outline.

I am sure that we have not heard the last of the "histiocyte," nor of its manifold speciations by monoclonal antibodies—despite Doctor Headington's enthusiastic obituary for it. The hearse may have arrived, but the cellular corpse is still warm and even a little febrile.

DR LORENZ E. ZIMMERMAN. I thank Doctor Jakobiec for this authoritative as well as erudite discussion that amplified my presentation so helpfully.

ADDENDUM

Since the presentation of this paper at the 1988 meeting, Case 2 has been the subject of a case report by SS Stopak, et al: "Sinus Histiocytosis Presenting As An Epibulbar Mass: A Clinicopathologic Case Report" (*Arch Ophthalmol* 1988; 106:1426-1428). It is included here with permission of Dr Morton Goldberg, Editor, *Archives of Ophthalmology*.