Eosinophilic granuloma of the orbit: A study of 8 cases

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Précis:

In our study of 8 cases with histopathology proven eosinophilic granuloma, Complete tumor resolution was achieved in 7 cases after receiving a mean of one intralesional steroid injection (median, 1; range, 1 to 2), while 1 patient was advised systemic chemotherapy for residual tumor.

Abstract:

Purpose: To describe the clinical presentation, treatment, and outcome of patients with eosinophilic granuloma of the orbit

Methods: Retrospective study of 8 patients

Results: All 8 patients in our series were males, and the mean age at presentation was 8 years (median 6 years; range, 7 months to 23 years). All of them had unilateral disease and the most common presenting complaint was upper eyelid swelling (n=6). The mean duration of symptoms was 6 weeks (median, 3 weeks; range 2 to 20 weeks). Visual acuity was unaffected in 7 cases. Clinical diagnosis included rhabdomyosarcoma (n=4), malignant lacrimal gland tumor (n=2), orbital cysticercosis (n=1), and orbital tuberculosis (n=1). The diagnosis of eosinophilic granuloma was confirmed by incisional biopsy (n=7) or fine needle aspiration cytology (n=1). Four cases underwent careful limited curettage and received intralesional steroid, and 4 cases were treated with intralesional steroid alone after incisional biopsy. Complete tumor resolution was achieved in 7 cases after receiving a mean of one intralesional steroid injection (median, 1; range, 1 to 2), while 1 patient was advised systemic chemotherapy for residual tumor. No tumor recurrence was noted in any case at a mean follow-up duration of 30 months (median, 23 months, range 7 to 96 months). None of the cases developed diabetes insipidus or multisystem disease during the follow-up period.

Conclusion: Eosinophilic granuloma is often misdiagnosed as a malignant tumor. Minimal intervention with intralesional steroids with/without careful curettage achieves complete tumor resolution.

Introduction:

Langerhans cell histiocytosis (LCH) represents a clonal proliferation of Langerhans cells in response to an unknown inciting stimulus and can be unifocal or multifocal.[1,2] The disease spectrum of LCH ranges from acute disseminated form (Letterer-Siwe syndrome) with lethal outcomes to chronic intermediate benign forms (Hand-Schüller-Christian disease and Langerhans cell histiocytosis) with favourable outcomes.[3] Eosinophilic granuloma is a form of orbital LCH which is associated with chronic inflammation that erodes into the surrounding bone mimicking malignant conditions.[4]

Eosinophilic granuloma of the orbit is a rare clinical entity and presents a diagnostic dilemma because of its radiological features. A detailed systemic work up is required to rule out multifocal/disseminated disease. Treatment options for localized orbital disease include surgical removal with bone curettage, intralesional corticosteroids and systemic chemotherapy in unresponsive cases.[4-9] Herein, we analyzed our experience and describe clinical features, radiological features, treatment modalities, and outcomes of eosinophilic granuloma of the orbit.

Materials and methods:

We retrospectively reviewed the clinical and histopathology records for "Eosinophilic granuloma" or "LCH" managed at the Ocular Oncology Service, L V Prasad Eye Institute, Hyderabad from January 2000 to January 2015. Inclusion criteria were histopathologically confirmed cases of eosinophilic granuloma with detailed systemic work-up (skeletal survey or bone marrow biopsy with bone scan, renal function tests, complete blood count, abdominal ultrasound and chest radiograph) as per guidelines of Histiocyte Society.[10] Institutional ethics committee approval was obtained and informed consent was available for all cases.

Medical records were analyzed for age at presentation, gender, laterality, symptoms, duration of symptoms, clinical features, differential diagnosis, radiological features, modality of treatment, histopathological features, and treatment outcome. Computed Tomography (CT) images of the orbit were reviewed from the photography archives. Medical oncologist examined all cases at initial presentation and systemic work-up (bone marrow biopsy with bone scan, renal function tests, complete blood count, abdominal ultrasound and chest radiograph) was done.

Management protocol was to perform incision biopsy to confirm the diagnosis of eosinophilic granuloma. After the histopathology confirmation of the diagnosis, the tumor was debulked and intralesional steroid triamcinolone acetonide (40mg/ml) was injected under general/local anesthesia.

Intralesional steroid injection was repeated after 4 weeks if there was any evidence of residual tumor. If the lesion showed no response to a minimum of three steroid injections, then low dose irradiation or systemic chemotherapy was administered as per medical oncologist opinion. Follow up was done 3-monthly for one year post resolution and yearly thereafter. Detailed systemic evaluation was done at each follow up visit by medical oncologist.

Results:

A total of 8 cases met the inclusion criteria (Table 1). All patients were males and the mean age at presentation was 8 years (median 6 years; range, 7 months to 23 years). All of them had unilateral disease with left eye being involved in 5 and right in 3 patients. The presenting complaints included swelling in the upper eyelid (n=6) and proptosis (n=2). The mean duration of symptoms was 6 weeks (median, 3 weeks; range 2 to 20 weeks). No incidental history of trauma or systemic illness could be elicited in any of the cases. There were no neurological symptoms.

All patients had proptosis (mean 4 mm) with limited elevation. Globe displacement was seen in 3 patients. Superior sulcus fullness was seen in all cases with palpable mass lesion documented in 2 cases. Visual acuity was unaffected in 7 cases. One case had vision less than 20/60 attributed to macular striae. There was no regional lymphadenopathy. Clinical diagnosis included rhabdomyosarcoma (n=4), malignant lacrimal gland tumor (n=2), orbital cysticercosis (n=1), and orbital tuberculosis (n=1). One patient with suspected orbital cysticersosis received a prior 2 weeks course of oral albendazole with no apparent clinical or radiological change. Contrast enhanced CT orbit revealed superiorly located well defined heterogenous mass with bony erosion involving frontal bone in 8, sphenoid in 1 and zygomatic in 1 patient. Mass effect with globe indentation was present in one case. Intracranial extension into anterior cranial fossa was seen in 5 cases and one case had temporal fossa involvement. (Figure 1)

All but one patient underwent orbitotomy via sub brow approach, by extraperiosteal route. After reflecting periosteum, incisional biopsy was performed from the mass lesion. In one case, fine needle aspiration cytology was done because of suspicion of adenoid cystic carcinoma of lacrimal gland. Intraoperative frozen section biopsy was performed in 4 cases and histopathological features were suggestive of eosinophilic granuloma. The diagnosis was confirmed on paraffin sections. These 4 cases were given intralesional steroid in the same sitting after debulking the tumor with limited curettage of the bone. The remaining 4 cases were given intralesional steroid after receiving histopathological confirmation of the diagnosis on paraffin sections. No postoperative complications were noted. Complete

resolution of proptosis was seen in all cases except one after receiving a mean of one intralesional steroid injection (median, 1; range, 1 to 3). Case 3 received 3 injections of triamcinolone 1cc (40mg/ml) with 60% reduction in tumor size. For residual disease, he was advised systemic chemotherapy. At the time of this manuscript preparation, the patient is still undergoing treatment with systemic chemotherapy with vincristine and cisplatin. Systemic workup was negative in all cases. There was no evidence for multifocal LCH in any case. None of the patients received radiation treatment. No tumor recurrence was seen in any case at a mean follow-up duration of 30 months (median, 23 months, range 7 to 96 months). None of the cases developed diabetes insipidus or multisystem disease during the follow-up period.

Intraoperative gross examination showed yellowish-white mass with necrotic appearance in all cases. All cases showed similar histopathological features (Figure 2). Light microscopic examination revealed highly cellular areas with small areas of necrosis and hemorrhage. A polymorphous population of cells was seen along with prominent histiocytes with abundant cytoplasm and a very prominent convoluted nucleus. In the background, multinucleated giant cells and inflammatory cells predominantly eosinophils along with neutrophils and lymphocytes were seen. Tumor cells showed diffuse expression of S-100 with positivity for CD1a. Histiocytes showed high expression of CD68.

Discussion:

Eosinophilic granuloma of the orbit is a rare form of LCH and mostly affects pediatric population in first decade of life as seen in our series.[2,3] It has a predilection for superior orbital rim. Frontal bone marrow remains active until second decade of life and may thus influence the tumor location.[5] Eosinophilic granuloma in adults is uncommon and most commonly affects the greater wing of sphenoid bone, where there is still active bone marrow in young adults.[11,12] In our series, there was only one adult patient (23 years of age), and the lesion was located in the frontal bone. The lesion is more common in boys than girls.[13] In our series, all patients were males.

Eosinophilic granuloma is usually unifocal with a benign course. Visual outcome is generally good as mass is located in anterior/mid orbit. All cases in our series had normal visual acuity at last follow up. Clinical differential diagnosis of orbital unifocal LCH includes rhabdomyosarcoma, Ewings sarcoma, neuroblastoma and inflammatory lesions involving bone like giant reparative granuloma of frontal bone, orbital tuberculosis.[2] Orbital mass with bony erosion and a progressive disease course presenting in first decade of life may raise a suspicion of malignant cause. Hence biopsy is indicated in

all cases, as no characteristic clinical or radiological features are pathognomonic of eosinophilic granuloma.

Orbital involvement along with systemic LCH was reported by Moore et al. in 18 of 76 (24%) children who were mostly managed with chemotherapy.[14] LCH is not a true neoplasm but an atypical proliferation of one cell population.[15] Langerhans cells are antigen-presenting cells, which mature from dendritic cells that are further derived from pluripotent stem cells found in bone marrow. These Langerhans cells mature in response to growth factors like colony stimulating factor. The triggering factors for such an aberrant immune interaction that leads to clonal proliferation of Langerhans cells is still unclear. Various factors like viral illness, genetic, and environmental factors have been implicated. Some authors postulate that dysregulated cytokine response in various immunodeficiency conditions like leukemia or viral illness leads to proliferation of pathologic Langerhans cells. These cells produce interleukin 1(Il-1) and prostaglandin E2 (PGE2) which have osteolytic activity.[16] Hence, bone destruction with soft tissue expansion is seen in almost all cases (100% in our series).

The treatment options of LCH include observation in sequential multifocal lesions, careful curettage/excision and intralesional steroids in primary unifocal lesions, low-dose radiation therapy for recurrences, chemotherapy for multifocal/recurrent disease, bone marrow transplantation in uncontrolled disease recurrences, and immunoglobulin therapy for central nervous system involvement.[17-19] Rare case scenarios of spontaneous resolution of unifocal orbital disease have also been reported.[20,21] Corticosteroids act in LCH by inhibiting the release of PGE2 and Il-1.[16] Harris et al reported a series of 6 cases with unifocal orbital LCH, in which 100% tumor resolution was achieved in 4 cases with subtotal curettage and intralesional steroid injection.[8,9] Nonorbital LCH involving bone also respond well to intralesional steroids. In a series of 35 cases of nonorbital LCH reported by Yasko et al, complete response was achieved in 89% cases with one intralesional injection and in 100% cases with two or more injections.[18] In our series, careful curettage and targeted therapy in the form of intralesional steroid injection achieved complete tumor resolution in 7 cases without systemic side effects. One case displayed incomplete response to multiple injections of intralesional steroids and was thus advised systemic chemotherapy.

Orbital involvement by LCH is considered as a risk factor for developing diabetes insipidus.[19] As per the guidelines of Histiocyte society, prophylactic systemic chemotherapy is recommended in cases with multisystem involvement of high-risk organs like liver, spleen, lungs and skull/orbital bones.[19] In the

LCH III study, all cases that developed diabetes insipidus had orbital involvement with multisystem disease.[19] In their protocol, the lesions in the orbital bones with intracranial soft tissue extension were regarded as "central nervous system (CNS)-risk" lesions, which may lead to CNS complications such as diabetes insipidus, and thus mandated systemic chemotherapy.[19] However, reports suggest that unifocal osteolytic lesions that arise in the anterolateral frontal bone and erupt into the orbital and intracranial cavities, undergo complete resolution after relatively minor local intervention, without the need for systemic chemotherapy.[2,8,9,22] In our study, none of the patients with intracranial extension (n=5) received systemic chemotherapy as primary treatment, and complete tumor regression was achieved with careful curettage and targeted therapy with intralesional steroid injection in 4 patients. Systemic chemotherapy was started in one patient due to incomplete response with steroids. None of the patients developed CNS complications or diabetes insipidus during the mean follow-up period of 18 months.

In summary, eosinophilic granuloma is a rare benign condition and is associated with aggressive bone destruction mimicking a malignant tumor. Minimal intervention in the form of careful curettage and intralesional steroids achieves complete tumor resolution.

References:

1. Moore AT, Pritchard J, Taylor DSI. (1985) Histiocytosis X: an ophthalmological review. Br J Ophthalmol;69:7-14.
2. Herwig MC, Wojno T, Zhang Q, Grossniklaus HE. Langerhans cell histiocytosis of the orbit: five clinicopathologic cases and review of the literature. Surv Ophthalmol 2013;58(4):330-40.
3. Writing Group of the Histiocyte Society. (1987) Histiocytosis syndromes in children. Lancet;1:208-9.
4. Harris GJ. (2006) Langerhans cell histiocytosis of the orbit: A need for interdisciplinary dialogue. Am J Ophthalmol;141:374-8.
5. Jakobiec FA, Trokel SL, Aron-Rosa D, et al. (1980) Localized Langerhans cell histiocytosis (Langerhans' cell histiocytosis) of the orbital frontal bone. Arch Ophthalmol;98:1814-1820.
6. Song A, Johnson TE, Dubovy SR, et al. (2003) Treatment of recurrent Langerhans cell histiocytosis with systemic therapy. Ophthal Plast Reconstr Surg;19:140–144.
7. Gunduz K, Palamar M, Parmak N, et al. (2007) Langerhans cell histiocytosis of the orbit: report of two cases. J AAPOS;11:506-8.
8. Harris GJ, Woo KI. (2003) Langerhans cell histiocytosis of the orbit: a paradox of aggressive destruction responsive to minimal intervention. Trans Am Ophthalmol Soc;101:93-103.
9. Woo KI, Harris GJ. Eosinophilic granuloma of the orbit: understanding the paradox of aggressive destruction responsive to minimal intervention. Ophthal Plast Reconstr Surg 2003;19(6):429-39.
10. Minkov M, Grois N, McClain K, et al. (2009) Langerhans Cell Histiocytosis. Histiocyte Society Evaluation and Treatment Guidelines. https://www.histiocytesociety.org/document.doc?id=290. Accessed 22 November 2015.
11. Zelger B. (2001) Langerhans cell histiocytosis: a reactive or neoplastic disorder? Med Pediatr Oncol;37:543-544.
12. Cheung N, Selva D, McNab AA. (2007) Orbital Langerhans cell histiocytosis in adults. Ophthalmology;114(8):1569-73.
13. Maccheron LJ, McNab AA, Elder J, et al. (2006) Ocular adnexal Langerhans cell histiocytosis clinical features and management. Orbit;25:169--77
14. Moore AT, Pritchard J, Taylor DS. (1985) Histiocytosis X: an ophthalmological review. Br J Ophthalmol;69:7—14.
15. Yu RC, Chu C, Buluwela L, et al. (1994) Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. Lancet;343:767—8.

16. Marusic A, Raisz LG. (1991) Cortisol modulates the actions of interleukin-1 alpha on bone formation, resorption, and prostaglandin production in cultured mouse parietal bones. Endocrinology;129:2699-2706.

17. Wirtschafter JD, Nesbit M, Anderson P, McClain K. (1987) Intralesional methylprednisolone for Langerhans' cell histiocytosis of the orbit and cranium. J Pediatr Ophthalmol Strabismus;24:194 –197.

18. Yasko AW, Fanning CV, Ayala AG, et al. (1998) Percutaneous techniques for the diagnosis and treatment of localized Langerhans-cell histiocytosis (Langerhans cell histiocytosis of bone). J Bone Joint Surg;80-A:219-228.

19. Helmut G, Nicole G, Milen M, et al. (2002) Histiocyte Society. LCH III (2nd version): treatment protocol of the Third International Study for Langerhans Cell Histiocytosis. https://www.skion.nl/workspace/uploads/lchiiiprot-version2.pdf. Accessed 22 November 2015.

20. Glover AT, Grove AS Jr. (1987) Langerhans cell histiocytosis of the orbit with spontaneous healing. Ophthalmology;94:1008-12.

21. Smith JH, Fulton L, O'Brien JM. (1999) Spontaneous regression of orbital Langerhans cell granulomatosis in a three-year old girl. Am J Ophthalmol;128:119-12.

22. Harris GJ, Woo KI. Is unifocal Langerhans-cell histiocytosis of the orbit a "CNS-Risk" lesion? Pediatr Blood Cancer 2004;43(3):298-9.

Legends:

Figure 1: Clinical presentation of Langerhans cell histiocytosis

(A) A 7-month-old child with superotemporal mass in right orbit

(B) Compited Tomography (CT) orbit revealed a soft tissue lesion in the superotemporal orbit with erosion of frontal bone

(C) Complete tumor resolution was achieved with careful limited tumor debulking along with intralesional triamcinolone acetonide

(D) A 23-year-old patient with left hypoglobus

(E) CT orbit revealed a superior orbital mass extending intracranially

(F) Complete tumor resolution was achieved with intralesional triamcinolone acetonide

Figure 2: Histopathology of Langerhans cell histiocytosis

(A) Photomicrograph shows prominent histiocytes with abundant cytoplasm against the background of mixed population of eosinophils and multinucleated giant cells (Hematoxylin and Eosin stain, 10x magnification)

(B) Eosinophils in the background (Hematoxylin and Eosin stain, 40x magnification)

(C) Histiocytes, lymphocytes, and eosinophils in the background (Hematoxylin and Eosin stain, 40x magnification)

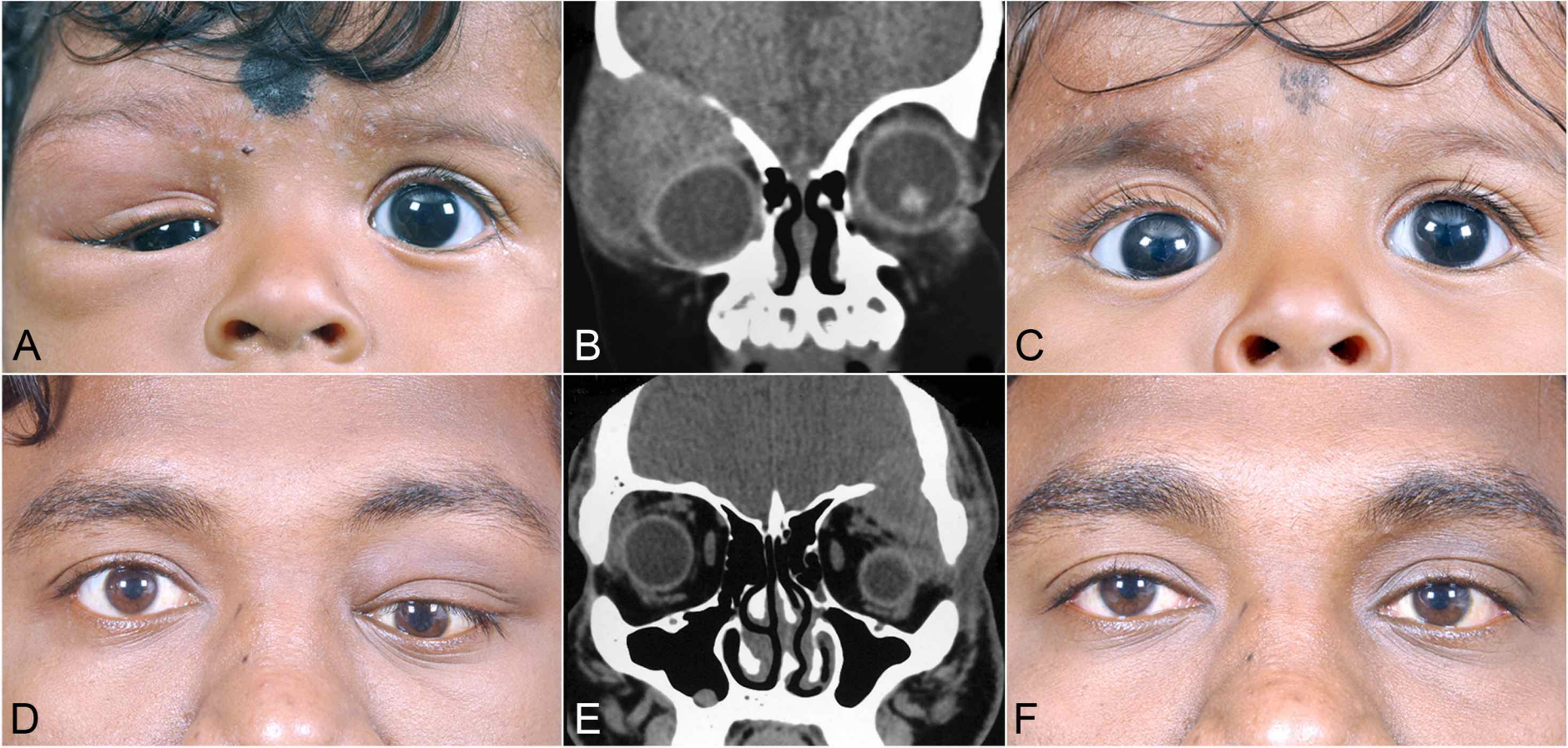
(D) Tumor cells displaying immunopositivity for CD1a (40x magnification).

Table 1: Summary of clinical details and treatment outcome of 8 patients with orbital eosinophilic granuloma

case	Age/Sex	Laterality	History	Location	Bone erosion	Extraorbital extension	Systemic involvement	Intralesional steroid (number of injections)	Outcome	Follow up (months)
1	7 months/M	OS	Swelling in upper eyelid since 2 months	Supero temporal	+	Intracranial	No	1	CR	12
2	1.5 years/M	OD	Swelling of both eyelids since 2 weeks	Superotemporal	+	Temporal fossa	No	2	CR	18
3	3 years/M	OS	Protrusion of eyeball since 2 weeks	Superomedial	+	Intracranial	No	3	Residual disease on systemic chemotherapy	7
4	3 years/M	OS	Swelling upper eyelid since 5 months	Superior	+	No	No	1	CR	24
5	8 years/M	OS	Outward protrusion since 2 weeks	Superior	+	Intracranial	No	1	CR	21
6	11 years/M	OD	Swelling upper eyelid since 4 weeks	Superior	+	Intracranial	No	1	CR	24
7	17 years/M	OD	Swelling upper eyelid since 2 weeks	Superior	+	Intracranial	No	1	CR	41
8	23 years/M	OS	Swelling upper eyelid since 1	Superior	+	No	No	1	CR	96

			month							

M=Male; CR=Complete resolution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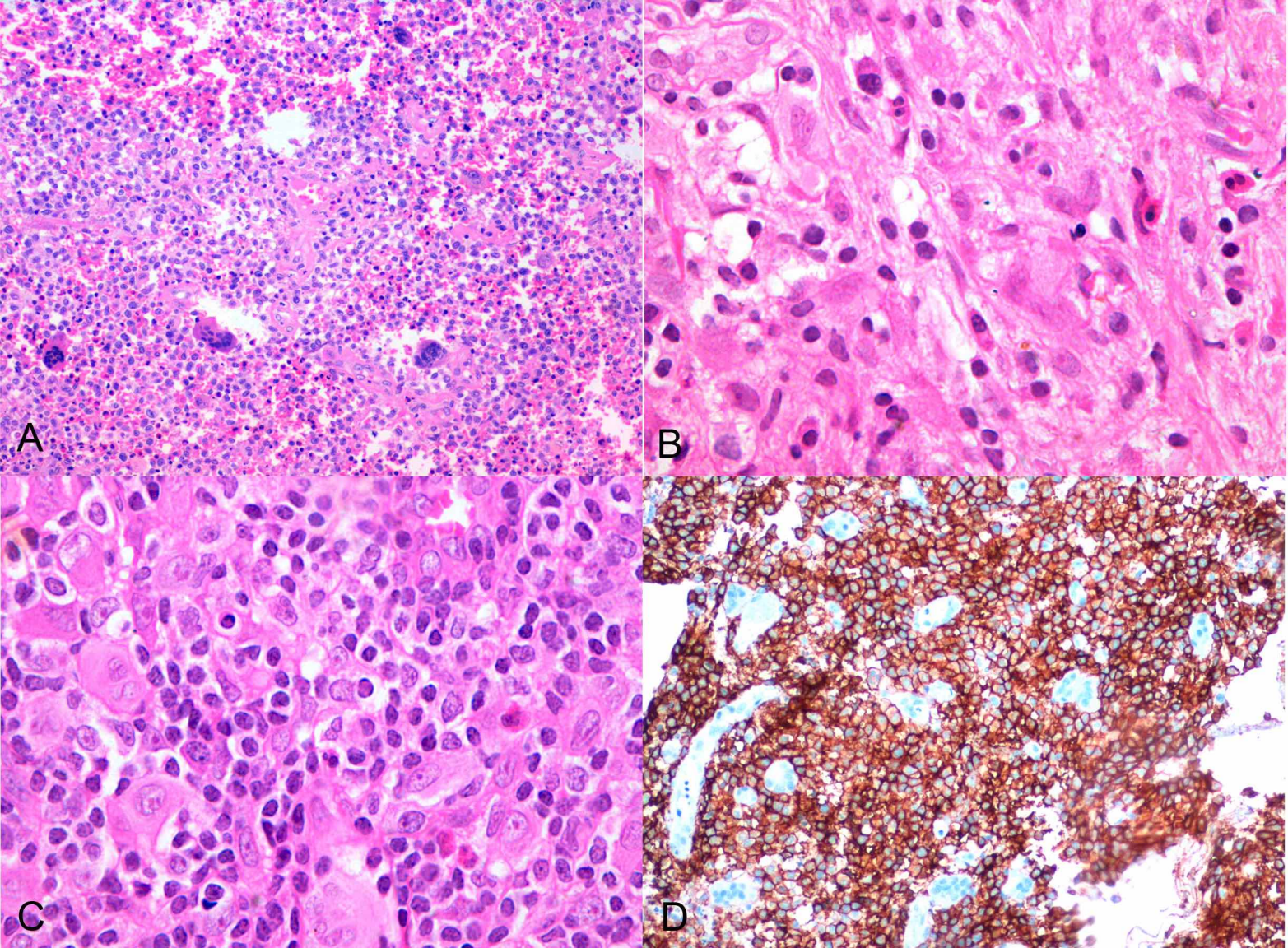
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