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GRANULOMATOUS DISEASES OF NOSE

Based on: Dhingra • K.K. Ramalingam • Logan Turner

INTRODUCTION

Definition

Granuloma — Definition

A granuloma is a focal, organised collection of activated macrophages (epithelioid cells) often surrounded by a rim of lymphocytes, formed as a chronic inflammatory response to a persistent antigen that the host cannot easily eliminate.

- Simplified: a tiny tissue 'ball' of immune cells walling off a chronic irritant (microbe, foreign body, or unknown antigen).

[VERY HIGH-YIELD] Granuloma = type IV (delayed) hypersensitivity reaction; characteristic of chronic inflammation.

Specific Granuloma

- Caused by a known specific organism with a characteristic histological pattern.
- Examples: Tuberculosis, Leprosy, Syphilis, Rhinoscleroma, Rhinosporidiosis, Fungal granulomas.

Non-specific Granuloma

- Histology not specific to any one organism.
- Includes foreign body granulomas and idiopathic granulomas.

Infective Granuloma

- Bacterial: TB, Leprosy, Syphilis, Rhinoscleroma.
- Parasitic/Fungal-like: Rhinosporidiosis.
- Fungal: Mucormycosis, Aspergillosis, Candidiasis.

Non-infective Granuloma

- Autoimmune: Wegener granulomatosis (GPA), Sarcoidosis.
- Idiopathic: Midline lethal granuloma, Cocaine-induced midline destructive lesion.
- Neoplastic: Extranodal NK/T-cell lymphoma, nasal type.

Autoimmune Granuloma

- Driven by aberrant immune response without identifiable organism.
- Granulomatosis with polyangiitis (GPA) and Sarcoidosis are the prototypes.

Destructive Midline Granulomatous Lesions

- Group of conditions producing progressive midfacial destruction.
- Includes GPA, NK/T-cell lymphoma (formerly 'lethal midline granuloma'), cocaine abuse, idiopathic midline destructive disease.

Granulomatous Tumour-like Lesions

- Polypoidal/fungating granulomas mimicking malignancy.
- Examples: Rhinosporidiosis, Rhinoscleroma (nodular stage), Lupus vulgaris.

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BASIC PATHOLOGY

Granuloma Formation — Stepwise Mechanism

- Step 1: Antigen persistence ? ingestion by macrophages.
- Step 2: Macrophages process antigen ? present to CD4? T-helper (Th1) cells.
- Step 3: Th1 cells release IFN-? and IL-2.
- Step 4: IFN-? activates macrophages ? transform into epithelioid cells.
- Step 5: Epithelioid cells fuse ? form multinucleated giant cells.
- Step 6: Surrounding lymphocytes + fibroblasts ? fibrous cuff ? mature granuloma.

[IMPORTANT] Granuloma formation = Type IV cell-mediated hypersensitivity.

Epithelioid Cells

- Modified, activated macrophages with abundant pale eosinophilic cytoplasm.
- Elongated nucleus resembling epithelial cells (hence 'epithelioid').
- Functionally specialised for secretion rather than phagocytosis.

Langhans Giant Cells

- Multinucleated cells with nuclei arranged at the periphery in a horseshoe/ring pattern.
- Characteristic of TB and other specific granulomas.

[COMMON MCQ] Langhans giant cells (peripheral nuclei) ? Langerhans cells (dendritic cells of skin).

Foreign Body Giant Cells

- Nuclei scattered randomly throughout cytoplasm.
- Formed around inert foreign material.

Caseation Necrosis

- Cheesy, friable, structureless eosinophilic necrosis.
- Hallmark of tuberculosis.
- Microscopically — amorphous granular debris with no preserved cellular outline.

Non-caseating Granuloma

- No central necrosis.
- Seen in: Sarcoidosis, Leprosy (tuberculoid type), Crohn's, foreign body, beryllium disease.

Vasculitis

- Inflammation and necrosis of vessel walls ? ischemia and tissue destruction.
- Classic in GPA — necrotising granulomatous vasculitis of small/medium vessels.
- Syphilis — obliterative endarteritis of vasa nervorum and small vessels.

Fibrosis

- End-stage of chronic granulomatous inflammation.
- Causes cicatricial stenosis (e.g., rhinoscleroma — fibrotic stage).

Tissue Necrosis

- Caseous (TB), gummatous (syphilis), coagulative (mucor — angioinvasion ? infarction).
- Determines clinical features: ulceration, perforation, deformity.

CLASSIFICATION OF GRANULOMATOUS DISEASES OF NOSE

Quick recall: INFECTIVE (bacterial / fungal / protistan) vs NON-INFECTIVE (autoimmune / idiopathic / neoplastic).

A. Infective Granulomas

Bacterial

- Tuberculosis (incl. Lupus vulgaris)
- Leprosy
- Syphilis
- Rhinoscleroma

Protistan / Parasitic-fungal

- Rhinosporidiosis

Fungal

- Mucormycosis
- Aspergillosis
- Candidiasis, Histoplasmosis (rare)

B. Non-infective Granulomas

Autoimmune / Vasculitic

- Wegener granulomatosis / Granulomatosis with Polyangiitis (GPA)
- Sarcoidosis

Idiopathic Midline Destructive Lesions

- Midline lethal granuloma (historical term)
- Polymorphic reticulosis
- Idiopathic midline destructive disease

Neoplastic

- Extranodal NK/T-cell lymphoma, nasal type

Toxin-induced

- Cocaine-induced midline destructive lesion (CIMDL)

[FAVORITE EXAM QUESTION] List the granulomatous diseases of the nose and classify them.

TUBERCULOSIS OF NOSE

Etiology & Types

- **Causative organism:** Mycobacterium tuberculosis (rarely M. bovis).
- **Primary nasal TB:** Direct inoculation ? rare; in patients without pulmonary disease.
- **Secondary nasal TB:** Most common; spread from active pulmonary TB via infected sputum.
- **Lupus vulgaris:** Cutaneous TB of the face/nose with low-virulence organism in a host with high immunity.
- **Tuberculoma:** Localised granulomatous mass of the nose.

Pathology

- Classic caseating epithelioid granuloma with Langhans giant cells.
- Site of predilection: anterior part of septal cartilage / anterior end of inferior turbinate.
- Septal cartilage involvement ? painless septal perforation (cartilaginous, anterior).

Lupus Vulgaris — Special Features

- Slowly progressive, chronic cutaneous TB.
- **Apple-jelly nodules:** Reddish-brown soft nodules visible on diascopy (glass slide pressure ? blanches surrounding redness, leaves apple-jelly translucent nodule).
- Sites: ala nasi, vestibule, columella, upper lip.
- Heals with scarring and disfigurement.

[VERY HIGH-YIELD] Apple-jelly nodules on diascopy = pathognomonic of LUPUS VULGARIS.

Cold Abscess

- Caseous material accumulates without acute inflammation ? painless, non-tender swelling.
- May involve nasal septum/dorsum.

Clinical Features

- Nasal obstruction (often unilateral early)
- Crusting and foul nasal discharge
- Ulceration of septum / vestibule
- Recurrent epistaxis
- Painless septal perforation (cartilaginous part)
- Constitutional: low-grade fever, night sweats, weight loss

Investigations

- **AFB stain (Ziehl-Neelsen):** acid-fast bacilli in smear/biopsy
- **Mantoux test:** positive (>10 mm induration)
- **PCR (CBNAAT / GeneXpert):** rapid and sensitive
- **Biopsy:** caseating granuloma with Langhans giant cells
- **Chest X-ray:** identify primary pulmonary focus
- ESR raised, HIV testing

Treatment

- **Anti-tubercular therapy (ATT) as per RNTCP/NTEP guidelines:**
- Intensive phase (2 months): HRZE (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol)
- Continuation phase (4 months): HRE

- Local nasal care: crust removal, alkaline douching.
- Reconstructive surgery once disease is quiescent.

LEPROSY OF NOSE

Etiology

- **Causative organism:** Mycobacterium leprae (acid-fast, weakly acid-fast, obligate intracellular).
- Nose is the earliest site involved and the main route of transmission via nasal droplets.

[IMPORTANT] Nasal mucosa is the EARLIEST site involved in leprosy and the principal source of infection.

Types

Lepromatous Leprosy (LL)

- Low host immunity ? multibacillary disease.
- Nasal mucosa heavily involved ? 'lepromatous rhinitis'.

Tuberculoid Leprosy (TL)

- High host immunity ? paucibacillary, non-caseating granulomas.
- Nasal involvement uncommon and milder.

Clinical Features

- Early: crusting, blood-stained discharge, nasal stuffiness ('snuffles' of leprosy).
- Atrophic rhinitis-like picture with foul-smelling crusts.
- Septal ulceration ? perforation (cartilaginous septum).
- Collapse of nasal dorsum ? saddle nose deformity.
- Anaesthetic nasal skin, loss of vibrissae, ala nasi destruction.

- Associated: leonine facies, madarosis (loss of eyebrows).

Pathology / Microscopy

- **Lepra cells (Virchow cells):** large foamy macrophages packed with M. leprae.
- **Globi:** clumps of bacilli inside lepra cells.
- Tuberculoid type: non-caseating epithelioid granulomas with nerve involvement.

Investigations

- Slit-skin smear / nasal smear: positive in lepromatous type.
- **Fite-Faraco stain (modified Ziehl-Neelsen):** demonstrates M. leprae.
- Biopsy from nasal mucosa or skin lesion.
- Lepromin test: positive in tuberculoid, negative in lepromatous.

[COMMON MCQ] Stain for M. leprae = Fite-Faraco stain (modified Ziehl-Neelsen using weaker decolouriser).

Treatment

- **Multi-drug therapy (WHO MDT):**

- Paucibacillary: Rifampicin + Dapsone × 6 months.
- Multibacillary: Rifampicin + Dapsone + Clofazimine × 12 months.

- Local nasal care: crust removal, douching.
- Reconstructive surgery: rhinoplasty for saddle nose; columellar reconstruction.

SYPHILIS OF NOSE

Etiology

- **Causative organism:** Treponema pallidum (spirochaete).
- Transmission: sexual (acquired) or transplacental (congenital).

Types

Congenital Syphilis

- **Congenital syphilitic rhinitis / 'Snuffles':** appears at 3rd–6th week of life.
- Persistent nasal discharge (initially watery, then mucopurulent ? bloody).
- Excoriation of upper lip, feeding difficulty.
- Late complications: saddle nose, palatal perforation, Hutchinson teeth.
- **Hutchinson Triad (late congenital syphilis):**

- Interstitial keratitis
- Sensorineural deafness (8th nerve)
- Hutchinson teeth (notched, peg-shaped upper central incisors)

[VERY HIGH-YIELD] Snuffles + saddle nose + Hutchinson triad = congenital syphilis.

Acquired Syphilis — Stages in Nose

- **Primary:** Chancre on nasal vestibule (rare).
- **Secondary:** Diffuse rhinitis with mucous patches; highly infectious.
- **Tertiary:** Gumma of nose and palate — characteristic destructive lesion.

Gumma

- Painless, rubbery granuloma of bone/cartilage.
- Common sites: hard palate, nasal septum (bony part), nasal bones.
- Breakdown ? palatal perforation and bony septal destruction.
- Bony septum involved ? saddle nose; palate involved ? oronasal fistula and hypernasal speech.

[IMPORTANT] TB causes CARTILAGINOUS (anterior) septal perforation; SYPHILIS causes BONY (posterior) septal destruction ? saddle nose.

Clinical Features

- Foul-smelling nasal discharge, crusting.
- Palatal perforation with hypernasal voice.
- Saddle nose deformity (collapse of nasal dorsum).
- Septal destruction with loss of supporting framework.

Investigations

- **Non-treponemal:** VDRL, RPR (screening; reactive in active disease).
- **Treponemal:** TPHA, FTA-ABS (confirmatory; remain positive lifelong).
- Dark-field microscopy of lesion exudate.
- Biopsy: gumma — central necrosis, plasma cell infiltrate, endarteritis obliterans.

Treatment

- **Drug of choice:** Benzathine Penicillin G IM.
- Early syphilis: 2.4 MU single dose.
- Late/Tertiary: 2.4 MU weekly × 3 doses.
- Penicillin allergy: Doxycycline / Ceftriaxone.
- Reconstructive surgery after disease control.

RHINOSCLEROMA

Etiology

- **Causative organism:** Klebsiella rhinoscleromatis (Frisch bacillus) — Gram-negative encapsulated bacillus.
- Endemic regions: Eastern Europe, Africa, Central/South America, parts of India.
- Affects nose, nasopharynx, larynx, trachea — collectively termed 'scleroma'.

Stages — Sequential Pathology

1. Catarrhal / Atrophic Stage

- Chronic purulent rhinitis with foul-smelling crusts.
- Resembles atrophic rhinitis.

2. Granulomatous / Nodular Stage

- Painless, rubbery, granulomatous nodules.
- 'Woody hard' indurated swelling of external nose and upper lip ('Hebra nose').

3. Cicatricial / Fibrotic Stage

- Dense fibrosis ? cicatricial stenosis of nasal vestibule, nasopharynx, subglottis.
- Causes airway obstruction.

Clinical Features

- Long-standing nasal obstruction, foul crusting, epistaxis.
- Painless hard swelling of nose and upper lip.
- Stenosis of nostrils/nasopharynx ? mouth breathing, hyponasality.
- Subglottic involvement ? stridor.

Histopathology

- **Mikulicz cells:** large foamy macrophages with central nucleus containing Klebsiella bacilli.
- **Russell bodies:** eosinophilic, refractile inclusions in plasma cells (immunoglobulin aggregates).
- Dense plasma cell infiltrate, fibrosis in late stage.

[FAVORITE EXAM QUESTION] Mikulicz cells + Russell bodies = RHINOSCLEROMA.

Investigations

- Biopsy with Warthin-Starry / Giemsa stain.
- Culture of Klebsiella rhinoscleromatis on MacConkey agar.
- CT scan: extent of disease and stenosis.

Treatment

- **Long-term antibiotics (3–6 months minimum):**
- Streptomycin + Tetracycline (classical)
- Ciprofloxacin / Rifampicin (modern alternatives)
- Surgery for stenosis: dilatation, scar excision, laser, stenting.
- Tracheostomy if subglottic airway compromise.

RHINOSPORIDIOSIS

Etiology

- **Causative organism:** Rhinosporidium seeberi — currently classified under Mesomycetozoea (protistan parasite, NOT a fungus).
- **Mode of infection:** pond bathing — contaminated stagnant water harbouring the organism.
- Endemic: South India, Sri Lanka.

[VERY HIGH-YIELD] Pond bathing ? Rhinosporidiosis. Most common site = NOSE (anterior septum / inferior turbinate).

Sites of Involvement

- Nose (most common — 70%)
- Nasopharynx
- Conjunctiva (palpebral)
- Lacrimal sac, larynx, skin, genitals (rare)

Clinical Features

- Painless progressive nasal obstruction.
- Strawberry-like friable polypoidal mass — pink/red, lobulated.

- Surface studded with white/yellow dots (mature sporangia visible through epithelium).
- Profuse bleeding on touch.
- Epistaxis, blood-stained discharge.
- Sessile or pedunculated.

CAUTION: AVOID incisional biopsy — extremely vascular lesion ? torrential bleed. Excisional biopsy with cautery is preferred.

Histopathology

- Mature sporangia containing thousands of endospores within the submucosa.
- Stains: H&E, PAS, GMS positive.
- No true mycelium ? distinguishes from fungi.

Treatment

- Wide surgical excision with electrocautery of the base — gold standard.
- Electrocautery destroys residual organisms ? prevents recurrence.
- Dapsone (100 mg/day × 6 months) — arrests maturation of sporangia; reduces recurrence.
- Recurrence prevention: avoid pond bathing, complete base cauterisation, postoperative dapsone.

FUNGAL GRANULOMATOUS DISEASES

Classification of Fungal Rhinosinusitis

Non-invasive

- Saprophytic fungal infection (surface colonisation of crusts).
- Fungal ball (mycetoma) — dense fungal mat in single sinus, immunocompetent host.

- Allergic fungal rhinosinusitis (AFRS) — IgE-mediated, eosinophilic mucin with Charcot-Leyden crystals.

Invasive

- Acute invasive (fulminant) — e.g., mucormycosis in DKA.
- Chronic invasive — slowly progressive, usually Aspergillus.
- Chronic granulomatous invasive — non-caseating granulomas, common in Sudan/India (A. flavus).

MUCORMYCOSIS (RHINO-ORBITO-CEREBRAL)

Etiology

- **Causative organisms:** Order Mucorales — Rhizopus (most common), Mucor, Rhizomucor, Lichtheimia.
- Ubiquitous saprophytic moulds; spores inhaled into nose/sinuses.

Predisposing Factors

- Uncontrolled diabetes mellitus, especially diabetic ketoacidosis (DKA).
- Immunocompromised states: haematological malignancy, neutropenia, transplant.
- Long-term corticosteroid therapy (notably post-COVID-19 mucormycosis surge).
- Deferoxamine therapy, iron overload.
- Burns, trauma.

[VERY HIGH-YIELD] DKA ? low pH ? free iron release ? Rhizopus thrives ? angioinvasion ? infarction.

Pathogenesis — Stepwise

- Step 1: Inhalation of sporangiospores ? germinate in nasal mucosa.

- Step 2: Hyphae invade vessel walls (angioinvasion).
- Step 3: Thrombosis ? ischemia ? coagulative necrosis ? BLACK ESCHAR.
- Step 4: Spread along vessels ? ethmoid ? orbit (via lamina papyracea) ? cavernous sinus ? brain.
- Step 5: Cranial nerve palsies, intracranial extension ? high mortality.

Clinical Features

- Unilateral facial pain, nasal stuffiness, blood-tinged discharge.
- Black necrotic eschar on turbinate / septum / palate.
- Palatal eschar with palatal perforation.
- Periorbital edema, proptosis, ophthalmoplegia, vision loss.
- **Orbital apex syndrome:** blindness + total ophthalmoplegia + V1 sensory loss.
- Cranial nerve palsies (II, III, IV, V, VI).
- Cavernous sinus thrombosis: bilateral chemosis, proptosis, fixed pupils.
- Intracranial spread: altered sensorium, hemiparesis, seizures, death.

Microscopy

- Broad, ribbon-like, aseptate (or pauci-septate) hyphae.
- Branching at right angles (90°).
- Stains: H&E, PAS, GMS, calcofluor white.

[COMMON MCQ] Broad + aseptate + right-angle branching = MUCOR. Septate + acute angle = ASPERGILLUS.

Investigations

- Diagnostic nasal endoscopy ? biopsy from black eschar.
- KOH mount + fungal culture (Sabouraud's dextrose agar).
- **CT PNS:** bone erosion, sinus opacification, periorbital extension.
- **MRI brain & orbit with contrast:** dural enhancement, cavernous sinus, intracranial spread.

- Blood glucose, ABG (for DKA), renal & liver function.

Treatment

- It is a MEDICAL + SURGICAL EMERGENCY.
- Correct underlying condition: aggressive control of DKA, stop steroids/immunosuppressants.
- **Systemic antifungals:**

- Liposomal Amphotericin B (5–10 mg/kg/day IV) — drug of choice.
- Posaconazole — oral step-down or salvage.
- Isavuconazole — alternative first-line.

- Aggressive surgical debridement of all necrotic tissue (FESS / open / orbital exenteration if needed).
- Retrobulbar amphotericin B injection in orbital disease.
- Multidisciplinary care: ENT + ophthalmology + neurosurgery + endocrinology + ID.

ASPERGILLOSIS

Etiology

- Aspergillus fumigatus (most common), A. flavus (granulomatous form), A. niger.
- Ubiquitous in soil, decaying vegetation.

Types

Non-invasive

- Fungal ball (aspergilloma): single sinus (commonly maxillary), immunocompetent.
- Allergic fungal rhinosinusitis (AFRS): atopic patients, eosinophilic mucin, nasal polyps.

Invasive

- Acute fulminant invasive: severely immunocompromised; angioinvasive — mimics mucor.
- Chronic invasive: slowly progressive over months.
- Chronic granulomatous invasive (primary paranasal): A. flavus, immunocompetent host, common in Sudan/India.

Clinical Features

- Nasal obstruction, foul discharge, headache.
- AFRS: nasal polyps + thick peanut-butter eosinophilic mucin + bony expansion of sinus.
- Invasive: proptosis, vision loss, cranial nerve palsies (slower than mucor).

Microscopy

- Septate hyphae with dichotomous branching at ACUTE angles (45°).
- Conidial heads with phialides ? conidia ('aspergillum' brush appearance).
- Stains: H&E, PAS, GMS.

Investigations

- CT PNS: hyperdense sinus contents with central calcifications, bony expansion (AFRS).
- MRI: hypointense on T2 (fungal contents, high iron/manganese).
- Serum total IgE, Aspergillus-specific IgE, fungal-specific IgG.
- Histopathology + KOH mount + culture.

Treatment

- Surgical clearance — FESS (gold standard for fungal ball and AFRS).
- AFRS: surgery + oral steroids + nasal steroid sprays + immunotherapy.
- **Invasive:** Voriconazole (drug of choice) ± surgical debridement.

- Alternatives: Isavuconazole, Liposomal Amphotericin B, Posaconazole.

WEGENER GRANULOMATOSIS / GRANULOMATOSIS WITH POLYANGIITIS (GPA)

Definition

A necrotising granulomatous vasculitis of small and medium-sized vessels, with a classical triad of upper airway, lung, and kidney involvement.

Classical Triad

- Upper respiratory tract (nose, sinuses, larynx)
- Lower respiratory tract (lungs)
- Kidneys (pauci-immune crescentic glomerulonephritis)

[VERY HIGH-YIELD] GPA TRIAD = ENT + Lung + Kidney = 'ELK'.

Clinical Features — Nasal

- Persistent nasal crusting with blood-stained discharge.
- Recurrent epistaxis.
- Septal perforation (bony or cartilaginous).
- Saddle nose deformity (collapse of nasal dorsum).
- Chronic sinusitis, anosmia.

Other ENT Manifestations

- Subglottic stenosis ? biphasic stridor, hoarseness.
- Otitis media with effusion ? conductive hearing loss; SNHL also possible.
- Facial nerve palsy.

Systemic Features

- Lung: nodules, cavitations, haemoptysis.
- Kidney: rapidly progressive glomerulonephritis (proteinuria, haematuria, red cell casts).
- Eye: episcleritis, scleritis, orbital pseudotumour.
- Skin: purpura, ulcers; CNS: mononeuritis multiplex.

Investigations

- **c-ANCA (PR3-ANCA):** positive in ?90% of generalised GPA — diagnostic hallmark.
- p-ANCA (MPO-ANCA): suggests microscopic polyangiitis (differential).
- Biopsy of nasal mucosa: necrotising granulomatous vasculitis (diagnostic but low yield).
- Lung biopsy: highest yield.
- Renal biopsy: pauci-immune crescentic GN.
- ESR, CRP raised; urinalysis (RBC casts); CT chest (cavitary nodules).

Treatment

- **Induction (severe disease):**
- High-dose corticosteroids + Cyclophosphamide OR Rituximab.
- **Maintenance:** Azathioprine / Methotrexate / Rituximab × 18–24 months.
- Plasma exchange — severe renal/pulmonary disease.
- Co-trimoxazole prophylaxis against PCP and disease relapse.
- Surgical: reconstruction of saddle nose after disease quiescent; dilatation/stenting of subglottic stenosis.

SARCOIDOSIS

Definition

Multisystem granulomatous disease of unknown aetiology characterised by non-caseating granulomas in affected tissues.

Pathology

- Non-caseating epithelioid granulomas.
- Asteroid bodies and Schaumann bodies within giant cells (non-specific).

Nasal Features

- **Lupus pernio:** violaceous, indurated nodular plaques on nose, cheeks, ears.
- Nodular mucosal lesions on septum and turbinates ('strawberry-skin' appearance).
- Nasal obstruction, crusting, recurrent epistaxis.
- Septal perforation, saddle nose (rare).

Systemic Features

- Bilateral hilar lymphadenopathy on chest X-ray.
- Pulmonary fibrosis, dyspnoea.
- **Heerfordt syndrome (Uveoparotid fever):**

- Uveitis
- Parotid enlargement
- Facial nerve palsy
- Low-grade fever

- Erythema nodosum, hypercalcaemia, anterior uveitis.

[FAVORITE EXAM QUESTION] Heerfordt syndrome = sarcoidosis. Lupus pernio = sarcoidosis (NOT lupus vulgaris which is cutaneous TB).

Investigations

- **Serum ACE (angiotensin-converting enzyme):** raised (supportive).
- Serum calcium: elevated.
- Chest X-ray / HRCT: bilateral hilar lymphadenopathy, reticulonodular shadows.
- Biopsy of mucosal lesion / lymph node / lung: non-caseating granuloma.
- Kveim test (historical, no longer used).
- Mantoux: typically negative (anergy).

Treatment

- Mild: observation; topical / intralesional steroids for skin/mucosal lesions.
- **Moderate/severe:** systemic corticosteroids (prednisolone 0.5–1 mg/kg/day).
- Steroid-sparing: Methotrexate, Azathioprine, Hydroxychloroquine, Infliximab.

MIDLINE DESTRUCTIVE LESIONS

Spectrum of Conditions

- Midline lethal granuloma (historical umbrella term)
- Polymorphic reticulosis (now considered a lymphoma)
- Idiopathic midline destructive disease (IMDD)
- Extranodal NK/T-cell lymphoma, nasal type — most cases of 'lethal granuloma'
- Cocaine-induced midline destructive lesion (CIMDL)

Common Clinical Presentation

- Progressive nasal obstruction, foul discharge, ulceration.
- Septal and palatal perforation.
- Facial tissue necrosis with midline destruction.
- Constitutional symptoms in lymphoma.

Extranodal NK/T-cell Lymphoma, Nasal Type

- Strongly associated with EBV (Epstein-Barr virus).

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- More common in East Asia and Latin America.
- **Immunohistochemistry:** CD2+, CD56+, cytoplasmic CD3+, EBER+ (EBV).
- Aggressive course, poor prognosis without treatment.
- Treatment: SMILE regimen (Steroid, Methotrexate, Ifosfamide, L-asparaginase, Etoposide) + radiotherapy.

Cocaine-Induced Midline Destructive Lesion (CIMDL)

- Chronic intranasal cocaine use ? vasoconstriction ? ischemic necrosis + secondary infection.
- Mimics GPA both clinically and serologically.
- Can be p-ANCA positive (atypical, anti-HNE antibodies) — diagnostic pitfall.
- Diagnosis: history of cocaine use + urine toxicology.
- Treatment: cessation of cocaine, supportive care, delayed reconstruction.

Differentiation — GPA vs CIMDL vs NK/T-cell Lymphoma

Feature	GPA	CIMDL	NK/T Lymphoma
Cause	Autoimmune vasculitis	Cocaine abuse	EBV-driven malignancy
Systemic	Lung + kidney	None	B-symptoms, marrow
ANCA	c-ANCA / PR3 +	Atypical p-ANCA (anti-HNE)	Negative
IHC	Granuloma + vasculitis	Non-specific necrosis	CD56+, EBER+

Treatment	Steroid + Cyclo/Rituximab	Stop cocaine	SMILE + RT

INVESTIGATIONS — CONSOLIDATED APPROACH

Clinical & Endoscopic

- Diagnostic Nasal Endoscopy (DNE): visualises crusts, ulcers, granulomas, polypoidal masses; guides biopsy.
- Biopsy site selection: edge of ulcer (active lesion), avoid heavily necrotic centre; avoid biopsy in rhinosporidiosis due to bleeding.

Laboratory

- CBC: anaemia, leucocytosis, eosinophilia (AFRS).
- ESR, CRP: raised in active inflammation/autoimmune disease.
- Mantoux test: TB screen.
- VDRL/RPR (screening) and TPHA/FTA-ABS (confirmatory): syphilis.
- c-ANCA / PR3-ANCA: GPA.
- p-ANCA / MPO-ANCA: microscopic polyangiitis (differential).
- Serum ACE: sarcoidosis (supportive).
- Serum calcium, IgE levels (AFRS), HIV testing.

Special Stains

- **AFB stain (Ziehl-Neelsen):** TB.
- **Fite-Faraco stain:** Leprosy (modified ZN).
- **Warthin-Starry:** Spirochaetes (Syphilis); also rhinoscleroma.
- **PAS, GMS:** Fungi, Rhinosporidium.

- **KOH mount:** rapid fungal screen.
- Calcofluor white: fungal hyphae fluorescence.

Microbiology

- Fungal culture: Sabouraud's dextrose agar.
- Bacterial culture: Klebsiella rhinoscleromatis on MacConkey agar.
- PCR / CBNAAT for TB; EBER in situ hybridisation for NK/T lymphoma.

Imaging

- **CT PNS (gold standard for sinus disease):** bone erosion, sinus opacification, calcifications (AFRS/aspergilloma).
- **MRI nose, PNS, orbit, brain:** soft tissue extent, orbital apex, cavernous sinus, intracranial spread (mucormycosis).
- Chest X-ray: pulmonary TB, GPA nodules, sarcoid hilar lymphadenopathy.
- HRCT chest: detailed pulmonary involvement.

COMPLICATIONS OF GRANULOMATOUS DISEASES

Local (Nasal)

- Septal perforation (cartilaginous: TB, leprosy; bony: syphilis, GPA).
- Saddle nose deformity.
- Palatal perforation (syphilis, GPA, mucor, NK/T lymphoma).
- Nasal stenosis (rhinoscleroma).
- Facial tissue necrosis (midline destructive lesions, mucormycosis).
- Recurrent epistaxis, anosmia, chronic sinusitis.

Airway

- Subglottic stenosis (GPA, rhinoscleroma) ? biphasic stridor.

- Airway obstruction may require tracheostomy.

Orbital

- Periorbital cellulitis, orbital abscess.
- Proptosis, ophthalmoplegia.
- Orbital apex syndrome (mucor).
- Blindness due to central retinal artery occlusion / optic neuropathy.

Intracranial

- Cavernous sinus thrombosis (mucor).
- Meningitis, cerebral abscess, infarction.
- Cranial nerve palsies — II, III, IV, V, VI.
- Death from intracranial extension (especially mucormycosis).

Systemic

- Pulmonary fibrosis (sarcoid, TB).
- Renal failure (GPA).
- Disseminated infection (leprosy, syphilis).

MANAGEMENT PRINCIPLES

Disease-Specific Drug Therapy

- **Tuberculosis:** ATT — 2HRZE + 4HRE (RNTCP/NTEP).
- **Leprosy:** WHO MDT — Rifampicin + Dapsone ± Clofazimine for 6–12 months.
- **Syphilis:** Benzathine Penicillin G IM (drug of choice).
- **Rhinoscleroma:** Long-term streptomycin + tetracycline OR ciprofloxacin × 3–6 months.
- **Rhinosporidiosis:** Surgical excision with cautery + Dapsone × 6 months.
- **Mucormycosis:** Liposomal Amphotericin B ? Posaconazole / Isavuconazole.

- **Aspergillosis:** Voriconazole (invasive); surgery for fungal ball/AFRS.
- **GPA:** Steroids + Cyclophosphamide / Rituximab.
- **Sarcoidosis:** Corticosteroids; steroid-sparing agents.
- **NK/T-cell lymphoma:** SMILE chemotherapy + radiotherapy.
- **CIMDL:** Cessation of cocaine, supportive care.

Role of Surgery

- Biopsy: tissue diagnosis is essential in all cases.
- Debridement: mucormycosis, invasive aspergillosis.
- Excision: rhinosporidiosis (with cautery of base).
- Airway: dilatation/stenting/tracheostomy for stenosis.
- Deformity correction: rhinoplasty for saddle nose, palatal obturator/repair — performed once disease is fully controlled.
- FESS: AFRS, fungal ball, sinus drainage.

IMPORTANT VIVA QUESTIONS

- Define granuloma and classify granulomatous diseases of the nose.
- Differentiate caseating vs non-caseating granuloma — give examples.
- What are apple-jelly nodules? Significance?
- Why does syphilis cause saddle nose but TB causes cartilaginous perforation without saddle nose?
- Name the cells diagnostic of leprosy and rhinoscleroma.
- Why is biopsy contraindicated in rhinosporidiosis?
- Stain used for M. leprae.
- Mode of acquiring rhinosporidiosis and most common site.
- Microscopic difference between Mucor and Aspergillus hyphae.
- Drug of choice for mucormycosis. What is angioinvasion?
- Classical triad of GPA. Investigation of choice?
- Heerfordt syndrome — components and diagnosis.

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- Differentiate GPA from cocaine-induced midline destructive lesion.
- Hutchinson triad — components.
- Stages of rhinoscleroma.
- Why is post-COVID mucormycosis common in India?

EXAM PEARLS — RAPID RECALL

[VERY HIGH-YIELD] Apple-jelly nodules = Lupus vulgaris (cutaneous TB).

[VERY HIGH-YIELD] Hutchinson triad = Interstitial keratitis + 8th nerve deafness + Hutchinson teeth.

[VERY HIGH-YIELD] Mikulicz cells + Russell bodies = Rhinoscleroma.

[VERY HIGH-YIELD] Strawberry mass with white dots + history of pond bathing = Rhinosporidiosis.

[VERY HIGH-YIELD] Broad, aseptate, right-angle branching hyphae = Mucor.

[VERY HIGH-YIELD] Septate, acute-angle (45°) branching hyphae = Aspergillus.

[VERY HIGH-YIELD] c-ANCA / PR3-ANCA = GPA. Triad: ENT + Lung + Kidney.

[VERY HIGH-YIELD] Lupus pernio + bilateral hilar LAD + raised ACE = Sarcoidosis.

[VERY HIGH-YIELD] Heerfordt syndrome (uveitis + parotid + facial palsy + fever) = Sarcoidosis.

[VERY HIGH-YIELD] Black eschar in DKA patient = Mucormycosis until proven otherwise.

[COMMON MCQ] Stain for M. leprae = Fite-Faraco (modified ZN).

[COMMON MCQ] Snuffles in newborn = Congenital syphilis.

[COMMON MCQ] Drug of choice — Mucor: Liposomal Amphotericin B; Aspergillus: Voriconazole.

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[FAVORITE EXAM QUESTION] TB ? cartilaginous (anterior) septal perforation. Syphilis ? bony septum + saddle nose + palatal perforation.

[FAVORITE EXAM QUESTION] Hebra nose = Woody hard external swelling of rhinoscleroma.

IMPORTANT TABLES

Table 1: Infective vs Non-infective Granulomas

Feature	Infective	Non-infective
Cause	Microbial	Autoimmune / idiopathic / neoplastic
Examples	TB, leprosy, syphilis, rhinoscleroma, mucor	GPA, sarcoidosis, NK/T lymphoma, CIMDL
Stain/Culture	Positive for organism	Negative for organism
Treatment	Specific antimicrobial	Immunosuppression / chemo

Table 2: Specific vs Non-specific Granuloma

Feature	Specific	Non-specific

Cause	Known organism	Unknown / foreign body
Histology	Characteristic pattern	Variable
Examples	TB, leprosy, syphilis, fungi	Foreign body, idiopathic

Table 3: Caseating vs Non-caseating Granuloma

Feature	Caseating	Non-caseating
Central necrosis	Present (cheesy)	Absent
Classic example	Tuberculosis	Sarcoidosis
Other examples	Histoplasmosis, syphilis (gumma)	Leprosy (TT), Crohn's, foreign body, beryllium

Table 4: Infective Granulomas — Comparative Chart

Disease	Organism	Hallmark Pathology	Treatment

TB	M. tuberculosis	Caseating granuloma, Langhans cells	ATT (2HRZE + 4HR
Leprosy	M. leprae	Lepra cells (foamy macrophages)	WHO MDT
Syphilis	T. pallidum	Gumma, endarteritis obliterans	Benzathine Penicillin
Rhinoscleroma	K. rhinoscleromatis	Mikulicz cells, Russell bodies	Strep + tetra / cipro
Rhinosporidiosis	R. seeberi	Sporangia with endospores	Excision + dapsone
Mucormycosis	Rhizopus / Mucor	Aseptate hyphae, angioinvasion	Lipo-AmB + debride
Aspergillosis	A. fumigatus / flavus	Septate hyphae, 45° branching	Voriconazole + surge

Table 5: TB vs Syphilis vs Leprosy of Nose

Feature	TB	Syphilis	Leprosy
Septum involved	Cartilage (anterior)	Bone (posterior)	Cartilage
Perforation	Painless, anterior	Painless, posterior	Anterior

Saddle nose	Uncommon	Common	Common
Pain	Mild	Painless gumma	Painless
Diagnostic test	AFB / GeneXpert	VDRL + TPHA	Slit-skin smear + Fite-Farac
Treatment	ATT	Penicillin	MDT

Table 6: Rhinoscleroma vs Rhinosporidiosis

Feature	Rhinoscleroma	Rhinosporidiosis
Organism	Klebsiella rhinoscleromatis	Rhinosporidium seeberi
Source	Endemic regions / overcrowding	Pond bathing
Lesion	Woody hard induration, stenosis	Strawberry polyp with white dots
Bleeding	Mild	Profuse — avoid biopsy
Microscopy	Mikulicz + Russell bodies	Sporangia with endospores

Treatment	Long-term antibiotics + surgery	Excision + cautery + dapsone

Table 7: Mucormycosis vs Aspergillosis

Feature	Mucormycosis	Aspergillosis
Organism	Rhizopus, Mucor	Aspergillus fumigatus/flavus
Host	DKA, immunocompromised	Variable (immunocompetent to compromised)
Hyphae	Broad, aseptate, 90° branching	Septate, acute-angle (45°) branching
Course	Acute, fulminant	Often chronic / indolent
Angioinvasion	Marked	Less prominent (except acute invasive)
Drug of choice	Liposomal Amphotericin B	Voriconazole

Table 8: GPA vs Sarcoidosis

Feature	GPA	Sarcoidosis
Granuloma	Necrotising, caseating-like	Non-caseating
Vasculitis	Present	Absent
ANCA	c-ANCA / PR3-ANCA +	Negative
ACE	Normal	Raised
Chest	Cavitary nodules	Bilateral hilar LAD
Kidney	Crescentic GN	Rare
Treatment	Steroid + cyclo / rituximab	Steroid ± methotrexate

Table 9: GPA vs Cocaine-induced Midline Destruction

Feature	GPA	CIMDL
Aetiology	Autoimmune vasculitis	Cocaine snorting

Systemic involvement	Lung, kidney +	Absent
ANCA	c-ANCA / PR3 +	Atypical p-ANCA (anti-HNE)
Urine toxicology	Negative	Positive for cocaine
Treatment	Immunosuppression	Stop cocaine; supportive

Table 10: GPA vs NK/T-cell Lymphoma

Feature	GPA	NK/T-cell Lymphoma
Nature	Autoimmune vasculitis	EBV-driven malignancy
IHC	Granuloma + vasculitis	CD2+, CD56+, EBER+
c-ANCA	Positive	Negative
Systemic	Lung + kidney	B-symptoms, marrow
Treatment	Steroid + cyclo / rituximab	SMILE + RT

Table 11: Special Stains in Granulomatous Nasal Diseases

Stain	Used For
Ziehl-Neelsen (ZN)	M. tuberculosis (AFB)
Fite-Faraco (modified ZN)	M. leprae
Warthin-Starry	Treponema pallidum, Klebsiella
Giemsa	Rhinoscleroma (Mikulicz cells)
PAS	Fungi, Rhinosporidium
GMS (Gomori methenamine silver)	Fungi (black hyphae)
KOH mount	Rapid fungal screening
Calcofluor white	Fungal hyphae (fluorescence)
EBER ISH	NK/T-cell lymphoma (EBV RNA)

Table 12: Drugs Used in Granulomatous Nasal Diseases

Disease	First-line Drug
Tuberculosis	HRZE (2 mo) ? HRE (4 mo)
Leprosy	Rifampicin + Dapsone ± Clofazimine
Syphilis	Benzathine Penicillin G
Rhinoscleroma	Streptomycin + Tetracycline / Ciprofloxacin
Rhinosporidiosis	Dapsone (after surgery)
Mucormycosis	Liposomal Amphotericin B
Aspergillosis (invasive)	Voriconazole
GPA	Corticosteroid + Cyclophosphamide / Rituximab
Sarcoidosis	Corticosteroid; Methotrexate
NK/T lymphoma	SMILE chemotherapy + RT

IMPORTANT DIAGRAMS / FIGURES

Pathology Diagrams

- Structure of a typical granuloma (epithelioid cells, Langhans giant cells, lymphocyte cuff, central necrosis).
- Caseating granuloma — labelled diagram (TB).
- Non-caseating granuloma — labelled diagram (sarcoidosis).
- Mechanism of vasculitis in GPA (necrotising granulomatous inflammation of vessel wall).

Clinical / Anatomical Diagrams

- Lupus vulgaris of nose — line diagram showing typical sites (ala, vestibule, columella).
- Apple-jelly nodules on diascopy — schematic.
- Gumma causing palatal perforation — sagittal section of palate and nose.
- Stages of rhinoscleroma — three-stage flowchart (catarrhal ? granulomatous ? cicatricial).
- Rhinosporidiosis polyp with white dots — labelled diagram.
- Saddle nose deformity — lateral profile diagram with mechanism (loss of dorsal support).
- Septal perforation — anterior view with cartilaginous vs bony comparison.
- Mucormycosis spread pathway — nose ? ethmoid ? orbit (lamina papyracea) ? cavernous sinus ? brain.
- Cavernous sinus anatomy with structures involved in CST.
- GPA saddle nose mechanism — septal vasculitis ? cartilage necrosis ? dorsal collapse.
- NK/T-cell lymphoma midline destruction — coronal view.
- Biopsy approach in granulomatous nasal lesion — algorithm flowchart.

Radiology Figures

- CT PNS — mucormycosis: opacified sinus with bone erosion, orbital extension.

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- MRI — invasive fungal disease: dural enhancement, cavernous sinus thrombosis.
- CT — AFRS: hyperdense sinus contents with bony expansion.
- Chest X-ray — bilateral hilar lymphadenopathy (sarcoidosis).
- Chest X-ray / CT — cavitary nodules (GPA).

IMPORTANT CLINICAL PHOTOGRAPHS

- Lupus vulgaris of nose — reddish-brown plaque on ala nasi.
- Apple-jelly nodules on diascopy — clinical photograph.
- Lepromatous facies — leonine appearance, madarosis, saddle nose.
- Syphilitic saddle nose deformity.
- Palatal perforation — intraoral view (syphilis / GPA / mucor).
- Rhinoscleroma — nasal stenosis with Hebra nose appearance.
- Rhinosporidiosis — strawberry-red friable polypoidal nasal mass with white dots.
- Mucormycosis — black necrotic turbinate on endoscopy.
- Mucormycosis — palatal eschar (black slough of hard palate).
- Orbital mucormycosis — proptosis, periorbital oedema, ophthalmoplegia.
- GPA — bloody nasal crusting and septal perforation.
- Cocaine-induced septal perforation with palatal involvement.
- NK/T-cell lymphoma — midline facial destruction.
- Endoscopic fungal debris (allergic mucin in AFRS, fungal ball).

IMPORTANT RADIOLOGY IMAGES

- CT PNS — black turbinate sign (early mucormycosis).
- CT PNS — bone erosion of medial orbital wall (invasive fungal disease).
- MRI brain — cavernous sinus thrombosis with intracranial extension (mucor).
- MRI orbit — orbital apex syndrome in mucormycosis.
- CT — hyperdense allergic mucin with bony expansion (AFRS).
- CT — fungal ball with central calcifications (aspergilloma).
- Chest X-ray — bilateral symmetrical hilar lymphadenopathy (sarcoidosis).

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- HRCT chest — cavitary lung nodules (GPA).
- Chest X-ray — apical fibrocavitary lesions (TB).

IMPORTANT MICROBIOLOGY / HISTOPATHOLOGY SLIDES

- Tuberculous granuloma — caseation + Langhans giant cells (H&E).
- AFB in nasal tuberculosis — Ziehl-Neelsen stain (red bacilli on blue background).
- Langhans giant cells — peripheral horseshoe nuclei (H&E).
- Fite-Faraco stain in leprosy — bright red bacilli within macrophages.
- Lepra cells / Virchow cells — foamy macrophages packed with bacilli.
- Syphilitic gumma — central necrosis with plasma cell rim.
- Syphilitic endarteritis obliterans — concentric intimal proliferation.
- Klebsiella rhinoscleromatis — Gram-negative encapsulated rods on Gram stain.
- Mikulicz cells — large foamy macrophages with central nucleus (rhinoscleroma).
- Russell bodies — eosinophilic refractile inclusions in plasma cells.
- Rhinosporidium seeberi — mature sporangia with endospores (PAS/H&E).
- Mucor — broad, ribbon-like, aseptate hyphae with right-angle branching (GMS/PAS).
- Aspergillus — septate hyphae with dichotomous acute-angle branching (GMS).
- GPA — necrotising granulomatous vasculitis of small/medium vessels.
- Sarcoidosis — non-caseating granuloma with asteroid/Schaumann bodies.
- NK/T-cell lymphoma — IHC: CD2+, CD56+, cytoplasmic CD3+, EBER+ ISH.

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