GRANULOMATOUS DISEASES OF NOSE

What is a Granuloma??

- Granulomas forms when the immune system attempts to wall off substances that it perceives as foreign but is unable to eliminate.
- Such substances include infectious organisms such as bacteria & fungi as well as other materials such as keratin & suture fragments (foreign body granuloma)

Histopathologically – A type of chronic inflammation characterized by concentric layers of cells consisting of specialized macrophages called **Epithelioid Cells** & **Multinucleated Giant Cells** surrounded by **lymphocytes & fibroblasts** (occasionally plasma cells); Necrosis & vasculitis could also be seen in varying degrees. However, the inflammatory process can be more diffuse without discrete classic granuloma formation.

2 types of granulomas include :

- **Foreign body granuloma** – do not produce any inflammatory or immune response & formed when the macrophages are unable to phagocytose the foreign body.
- **Immune granuloma** – due to inciting of inflammatory or immune response.

Classification :

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<th>NEOPLASTIC</th>
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<td>T Cell Lymphoma (Midline Lethal Granuloma)</td>
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<td>Aspergillosis</td>
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Rhinosporidiosis
Zygomycosis
Blastomycosis
Sporotrichosis
PROTOZOA –
Leishmaniasis

Infective Granulomatous Conditions of Nose

Tuberculosis:

- **Portal of Entry** – Inhalation (Most common), Ingestion or Inoculation.
- Almost always associated with **Primary Pulmonary Tuberculosis**.
- **Main Pathogens** – Mycobacterium Tuberculosis & M. Bovis
- MC type affecting Nose is **Lupus Vulgaris / Tuberculosis Luposa / Cutaneous Tuberculosis**.

**LUPUS VULGARIS**

- Cutaneous tuberculosis associated with painful skin lesions most often on the face around the nose, eyelids, lips, cheeks, ears & neck.
- **Macroscopic appearance**:
  1. Nodular form (Most Common)
  2. Ulcerative form
  3. Sinus granuloma

**NODULAR FORM:**

- **Indolent & Chronic** form
- Affects skin & mucous membrane of nose.
- Young Female : Male = 2:1
- Temperate climate > In Tropics.
- Usually begins in the **Vestibule** (M.C. site = Mucocutaneous Junction of the nasal septum) & then extends to the adjoining skin & mucosa.
- Due to **Direct Inoculation** into the dermis in a patient who otherwise has strong immunity to the infection, usually due to a previous exposure.
Lupus is also known to cause extensive scarring of the vestibule leading on to its distortion. Nasal lesions are frequently associated with or could be considered to be precursor to nodules on the face.

**HISTOPATHOLOGY**

- **Tuberculous granuloma**
  - In the center these lesions show collection of reticuloendothelial cells. These cells soon necrose & coalesce. **Necrotic center** is surrounded by a ring of living **RE cells** which further are surrounded by ring of **Lymphocytes, Plasma Cells & Fibroblasts**. Giant cells are found scattered throughout the tubercle & are usually multinucleated.

**SYMPTOMS**

1. Nasal discharge
2. Nasal obstruction
3. Presence of non-foul smelling crusts
4. Epistaxis
5. Evening rise of temperature
6. When there is ulceration then there could be mild fetor.
7. The typical early lesion in the nose is a reddish firm nodule at the mucocutaneous junction of the nasal septum. These nodules are known as “**Apple Jelly Nodules**” since they resemble apple jelly in their appearance.
8. Pain is unusual.
9. The nodules may coalesce & break down to form characteristic ulcers with a pale granular base & undermined edges

**DIAGNOSTIC FEATURES OF LUPUS NODULES:**

1. Blanching
2. Bacterial examination
3. Biopsy

- **Blanching** – To highlight the apple jelly nodules, blood should be expressed from adjoining tissues by applying pressure with a glass slide, this will make the pinkish lupus nodules to stand out in contrast.
- **Bacteriological examination** may demonstrate Acid Fast Bacilli.
- Culture of the organism – Lowenstein-Jensen slope, Culture can now be accelerated by the use of recent technology, such as **BACTEC**.
- **Biopsy** is always diagnostic.

**COMPLICATIONS:**

- Pulmonary tuberculosis
- Dacryocystitis, Corneal Ulceration, Nasopharyngeal Lupus
- Lupus Of Face
- Atrophic Rhinitis
Development Of Epithelioma (Rare Sequelae)

Sudden increase in size & hardness of the node in an elderly with an increasing tendency to bleed should arouse the suspicion of epithelioma formation. Biopsy is an absolute indication in these cases.

ULCERATIVE FORM:

Ulcers are commonly found on the anterior part of the nasal septum, inferior turbinate & anterior choanae.
This usually involves the cartilaginous nasal septum or the inferior turbinate.
Ulceration of nasal mucosa is usually followed by fibrosis & contraction causing distortion of alae nasi.
If turbinates are involved extensively, the lining ciliated columnar epithelium is not renewed. This could lead on to the formation of secondary atrophic rhinitis.
In advanced cases of lupus the floor of the nasal cavity & turbinates can also be involved, the spread usually occurring in a backward direction from the primary site.
Septum may also undergo perforation, but in these cases classically the cartilaginous portion alone is involved & hence there is no sinking of the nasal bridge. This is in sharp contrast to syphilitic involvement of nasal septum where in destruction is confined only to the bony portion of the nasal septum, with an intact cartilaginous portion. In leprosy both bony & cartilaginous portions of nasal septum is destroyed associated with sinking of nasal bridge.

<table>
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<tr>
<th>LUPUS VULGARIS</th>
<th>SYPHILIS</th>
<th>LEPROSY</th>
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<tr>
<td>Cartilagenous Involvement</td>
<td>Bony Involvement</td>
<td>Both Bony &amp; Cartilagenous Involvement</td>
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SINUS GRANULOMA

Isolated sinus involvement may occur without any signs or symptoms in the nose. In previous years, this form usually presented with a diffuse soft tissue swelling & multiple discharging sinuses in the supraorbital region secondary to osteomyelitic involvement of the frontal bone.
Involvement of the orbit & its nerves may occur.
CT & MRI are nonspecific – demonstrate a soft tissue mass with or without bone destruction
The diagnosis is established by an External or Endoscopic Biopsy.

SPECIFIC INVESTIGATIONS:

Montaux test, AMTD (Amplified Mycobacterium Tuberculosis Detection), PCR, Fluorescence microscopy
AMTD - uses principles of transcription mediated amplification of rRNA of Mycobacterium TB. Detection of tRNA indicates the presence of actively multiplying MTB.

TREATMENT:
This condition responds well to antituberculous drugs.

**SHORT COURSE CHEMOTHERAPY:**

- Extends over 6-9 months & consists of Rifampicin, INH, Ethambutol & Pyrizinamide.

**DOTS**:
- Initial Phase - 2 mths - HRZE
  - i. Rifampicin (R) - 450mg (additional 150 mg if > 60kg)
  - ii. INH (H) - 600mg
  - iii. Ethambutol (E) - 1200mg
  - iv. Pyrizinamide (Z) - 1500mg
- Maintenance treatment (4 months) - (HR)3 (thrice weekly under observation)
- Vit D supplementation appears to hasten sputum culture conversion (only in Vit D deficient cases).
- After the disease is arrested surgical repair of the deformed nose can be carried out.

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<th>New Cases*</th>
<th>Previously treated Cases**</th>
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<tr>
<td>New sputum smear-positive, New sputum smear-negative, New extrapulmonary tuberculosis, others</td>
<td>Sputum smear-positive relapse, Sputum smear-positive failure, Sputum smear-positive after default treatment, others</td>
</tr>
</tbody>
</table>

\[ 2H_3R_3Z_3E_3 + 4H_3R_3 \]  
\[ 2H_3R_3Z_3E_3 + 1H_3R_3Z_3E_3 + 5H_3R_3E_3 \]

2 months intensive phase + 4 months continuation phase  
3 months intensive phase + 5 months continuation phase

Four drugs at Thrice-weekly Schedule for 2 months Intensive phase  
Five drugs at thrice-weekly Schedule for initial 2 months followed by Four drugs for next 1 month Intensive phase. Three drugs at Thrice-weekly Schedule for remaining 5 months continuation phase.

H: *Isoniazid* (600 mg), R: *Rifampicin* (450 mg), Z: *Pyrazinamide* (1500 mg),  
E: *Ethambutol* (1200 mg), S: *Streptomycin* (750 mg)

1. Patients who weigh 60 kg or more receive additional Rifampicin 150 mg.
2. Patients who are more than 50 years old receive Streptomycin 500 mg. Patients who weigh less than 30 kg receive drugs as per Pediatric weight boxes according to body weight.
LEPROSY

Causative Organisms – M. Leprae.
This bacterium is more or less morphologically similar to M. Tuberculi.
Although M. Leprae cannot yet be cultured on an artificial medium, it can nevertheless
be inoculated into experimental animals, particularly immunologically deficient mice, to
produce a disease similar to that in man.
Based on the Host's Immunological Status & Clinical, Histological & Microbiological
features leprosy divided into types.

**TYPES OF LEPROSY:**

<table>
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<tr>
<th>LEPROSY TYPE</th>
<th>CHARACTERISTICS</th>
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| Tuberculoid leprosy (TT) or paucibacillary leprosy (PB) | ✓ Vigorous host resistance & low infection  
✓ A localized disease in patients with high cell-mediated immunity characterized by a single, clearly demarcated hypopigmented/anaesthetic skin area of the face, h&s or feet, with thickening of the subserving sensory or motor nerves.  
✓ This could lead on to paralysis of muscles.  
✓ Skin lesions may extend up to the nasal vestibule.  
✓ This type of lesion falls short without involving the nasal mucosa.  
✓ Isolated cranial nerve palsies (V & VIIth) have also documented in this type of leprosy. |
<p>| Borderline Tuberculoid Leprosy (BT) | ✓ As TT, but more numerous, smaller skin lesions with thickening of peripheral nerves &amp; deformity of the h &amp;s&amp; feet |
| Borderline Leprosy (BB) | ✓ Numerous skin lesions of varying size &amp; form (macules, papules, plaques) with punched-out, hypopigmented anaesthetic centres; widespread nerve involvement &amp; limb deformity |
| Borderline Lepromatous | ✓ Large number of florid asymmetrical skin lesions of |</p>
<table>
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<tr>
<th>Leprosy (BL)</th>
<th>variable form, strongly positive to acid-fast bacilli</th>
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| Lepromatous leprosy (LL) or Multibacillary Leprosy (MB) | ✓ Severely compromised host resistance & massive infection  
✓ In this type of leprosy there is diffuse infiltration of skin, nerves & mucosal surfaces by the bacteria.  
✓ Cutaneous infiltration is more common over the edges of pinna, chin, nose & eyebrows because these areas have a temperature lesser than that of core temperature.  
✓ These patients are considered to be highly infectious, as their nasal discharges contain potentially infectious lepra bacilli.  
✓ Commonly the affected nose has crust formation, nasal obstruction & Sero sanguineous discharge.  
✓ The earliest sign of nasal mucosal involvement is the presence of **nodular thickening** of nasal mucosa.  
✓ These nodules are paler than the surrounding mucosa with a yellowish tinge.  
✓ These lepra nodules commonly begin at the anterior end of inferior turbinate, it then progresses to gross inflammation of nasal mucosa.  
✓ Nasal obstruction is out of proportion to that of degree of nasal mucosal involvement. This is due to the fact that the nasal valve area is commonly affected.  
✓ Both the **bony & cartilaginous portions** of nasal septum are destroyed due to perichondritis & periosteitis.  
✓ **Nasal bridge collapse** is commonly seen in these patients. **Anterior nasal spine** is commonly destroyed in these patients.  
✓ **Hyposmia** is seen in 40% cases of lepromatous leprosy.  
✓ Glove-&-stocking Anaesthesia, Gynaecomastia, Testicular Atrophy, Ichthyosis, Nerve Palsies & Neurotrophic Resorption of the Phalanges.  
✓ **Lucio's phenomenon** (endarteritis & ulceration) is noted in Mexico & Central America.  
✓ **Radiographs** showing the absence / erosion of **anterior nasal spine** are virtually diagnostic of Lepromatous leprosy.  
✓ Diagnosis can always be confirmed by studying the scrapings of nasal mucosa. They demonstrate the typical **Cigar Pattern Lepra Bacilli**.  
✓ Commonly positive scrapings can be obtained from the
Borderline leprosy:

These patients have poor immunological resistance. They may hence progress to Lepromatous type. Skin lesions are more numerous & are seen around eyes, nose & mouth. In pure borderline lesions involvement of nasal mucosa is not seen. If nasal mucosal involvement is demonstrated than it will have to be assumed that the lesion has progressed to Lepromatous stage.

DIAGNOSIS:

- Diagnosis of leprosy is usually made on the clinical findings of anaesthesia on the skin, thickened peripheral nerves & skin lesions, & is supplemented by bacteriological examination.
- Early diagnosis is essential since nasal discharge is principle route of transmission of the disease.
- Diagnosis is confirmed by demonstration of M. leprae on microscopy of the nasal discharge or scrapings of nasal mucosa, or histopathology of nasal mucosa.
- In tuberculoid or intermediate leprosy, a skin biopsy may be required to demonstrate the bacillus.

TREATMENT:

Dapsone is the sheet anchor drug used in the management of leprosy. It virtually reduces the bacilli count of nasal discharge to zero or near zero within a couple of months. But there is an increased development of resistance to the drug. Modern drugs like Rifampicin & Clofazimine can reduce the bacilli count to zero within 10 days.

Triple therapy:

1. Rifampicin – 600 mg on first two days of a month taken before breakfast
2. Clofazimine – 100 mg on alternate days i.e. three times a week
3. Dapsone – 100 mg a daily.

Direct intranasal administration of rifampicin has been noted to reduce the M. Leprae load in the nose much faster than when the drug was given by the oral route.

These drugs are continued for 3 months after which Rifampicin is stopped. Other two drugs are continued till 9 months are completed. Nasal douching with saline will help in removal of crusts.

Betnovate (1 part) in Unguentum (2 parts) has been used with good results.
SYPHILIS:

- Nasal syphilis can affect any age group from the neonate to the elderly.
- The disease is no longer common & the signs & symptoms in the early stages may be difficult to elicit, particularly if antibiotics have already been given.
- Causative Organism — Treponema Pallidum (a Spirochete)
- Mode of transmission — Contact with an infectious sexual partner (moderate risk).
- The organisms usually reside & multiply in the perivascular lymphatics of the blood vessel wall.
- The local host reaction results in an infiltration by polymorphs, activated lymphocytes (CD4+ & CD8+), plasma cells & histiocytes which are typical of syphilis.
- The resultant Endarteritis of small blood vessels with secondary hypertrophic changes in the endothelium, may lead to Endarteritis Obliterans & Luminal Obliteration.

HISTOPATHOLOGY:

- Diagnosis is purely Histopathological. It is characterized by Oedema, Stromal Infiltration with Lymphocytes, Plasma cells & Endothelial cells.
- Perivascular cuffing by these cells & endarteritis will cause a reduction in the lumen of blood vessels causing necrosis & ulceration.

Nasal syphilis can be classified into:

1. Primary syphilis
2. Secondary syphilis
3. Tertiary syphilis

PRIMARY SYPHILIS:

Also known as chancre can occur at the external nose or inside the vestibule. It appears as a hard, non-painful ulcerated papule always associated with enlarged, rubbery, & non-tender lymphadenopathy. A sore or chancre develops at the site of inoculation 10-90 days (average 21 days) following infection. There may also be associated systemic features like fever & malaise. These lesions undergo spontaneous resolution within 6-10 weeks.

This condition should be differentiated from malignant neoplasms & furunculosis. Malignant neoplasms are relentless in their progression, & affect older age group patients. Furunculosis is rather painful condition & followed by suppuration. These patients will respond to anti syphilitic treatment. I.e. Intramuscular injections of penicillin. The chancre may be cleansed with 1:2000 solution of HgCl & the surface smeared with 2% yellow mercuric oxide ointment.
The following points should be borne in mind:

1. Cultures from the surface of the lesion will always be negative
2. Smears when examined under dark ground illumination will show the spirochete Treponema palladium
3. **Serological tests** for syphilis may be positive – VDRL, TPHA, FTA-ABS. (The VDRL is a nontreponemal test & is relatively nonspecific but becomes positive early (4 - 5 weeks) & correlates well with disease activity.)
4. A biopsy from suspicious lesion may confirm the diagnosis

**SECONDARY SYPHILIS:**

This is the most infectious of all the three stages of syphilis. Symptoms usually occur appear **6-10 weeks** after inoculation. Secondary syphilis is rarely recognized in the nose, as mucous patches hardly ever occur on such a thin, attenuated mucous membrane. The symptoms include:

1. Simple catarrhal rhinitis (persistent)
2. Crusting & fissuring of nasal vestibule
3. Other secondary lesions like mucous patches in the pharynx are also seen
4. Roseolar / papular skin rashes
5. Shotty enlarged non tender lymph nodes.
6. The scar of the primary lesion in the genitals or elsewhere may be visible.

Serological tests for syphilis are positive. These patients respond to antisyphilitic drugs

Dark-field examination of moist or intentionally abraded dry lesions may demonstrate the organism. Lymph node aspirates or tissue specimens (lymph nodes, liver, skin or mucous membrane) may also be examined by **Silver Stains** or **Immunofluorescence** for detection of spirochetes.

**TERTIARY SYPHILIS:**

Though only approximately **1/3rd** of cases with secondary syphilis progress to show clinical manifestations of tertiary syphilis this stage is commonly encountered in the nose. The lesion is also known as **Gumma.** This lesion invades the mucous membrane, periosteum & bone. The bony portion of the nasal septum is frequently affected causing septal perforation.

Rarely the following portions of the nose can also be involved:

1. Lateral nasal wall
2. Frontal sinus
3. Nasal bones
4. Floor of the nose

**SYMPTOMS**
1. Pain / headache (worse during night).
2. Swelling / obstruction of nose – Swelling may be diffuse / localized associated with offensive discharge, bleeding & crusting of the nose
3. Olfactory Acuity Diminishes.
4. Perforation of bony portion of nasal septum associated with collapse of the bridge of the nose can cause structural damage to the nasal architecture.
5. There may also be associated **Secondary Atrophic Rhinitis**
6. The lesion is usually unilateral, but if septum is involved then swelling may be present in both sides of the nasal cavity.
7. **Tenderness over the bridge of the nose** is a characteristic sign

**DIAGNOSIS**

The following points aids in the diagnosis:

1. The swollen nasal mucosa does not shrink when vasoconstrictors are used
2. Radiographs show rarefaction of bone with blurring of the cortical outline
3. Serological tests for syphilis are positive in a vast majority of cases
4. Biopsy from the lesion is diagnostic

Diagnosis of tertiary syphilis may be made from a combination of characteristic organ involvement, the histopathological picture, reactive non treponemal & treponemal serological tests & response to adequate antibiotic therapy.

**COMPLICATIONS**

Nasal complications of Gumma:

1. Secondary infections with pyogenic organisms
2. Sequestration
3. Perforation of bony portion of nasal septum, palate or nasal walls
4. Collapse of bridge of nose with deformity of nose
5. Scarring / stenosis of nasal passages
6. Atrophic rhinitis
7. Intracranial complications due to involvement of meninges.

**TREATMENT:**

2. Local treatment – Clearance of crusts & regular cleansing of the nasal passages by copious alkaline douches one to three times a day.
3. **Yellow Mercury Oxide** Ointment may be applied locally. **Dilute Mercuric Nitrate Ointment** should be applied freely to the nasal vestibules.
4. **Gummas** respond rapidly to general **antisypillitie** treatment but **atrophic rhinitis & deformity may persist** after the disease is cured & this may need further surgery.

**CONGENITAL SYPHILIS “SNUFFLES”**:
In congenital syphilis any of the lesions of secondary & tertiary forms of syphilis of nose can occur.

In infants these lesions classically begin during the 3rd week (21 days) of life. These lesions may also appear even as late as 3 months of life. At first snuffles appear as Simple Catarrhal Rhinitis.

In very short time it becomes purulent with secondary fissuring & excoriation of the nasal vestibule & upper lip.

Since infants are obligate nasal breathers, the obstruction may even lead to feeding problems.

Gummatous & destructive lesions occur most commonly at puberty.

Mucous membrane, periosteum & bone may all be affected.

The resulting ulceration & destruction ultimately lead to features of secondary atrophic rhinitis & sinking of the nasal bridge, producing the Saddle Nose Deformity.

Other stigmata of syphilis, particularly Hutchinson's Incisors, Interstitial Keratitis & Moon's molars, Corneal Opacities & Sensorineural Deafness (CurSE HIM) may be present, & there may be a family history of syphilis, miscarriages & still births.

Serologic tests for syphilis will invariably be Negative. Priority should be given to the management of nasal obstruction in these patients.

**TREATMENT OF CONGENITAL SYPHILIS**

- In snuffles, the airway must be restored for suckling.
- The nasal discharge is removed by gentle suction & irrigation & the use of local drops of 0.5 percent ephedrine solution or simple normal saline, & by hyper extending the head before feeding.
- In the tertiary forms, simple nasal toilet by syringing with isotonic alkaline douche solution will remove the crusts & discharge, & Yellow Mercuric Oxide Ointment may be applied frequently to the nasal vestibules.

**YAWS (FRAMBOESIA):**

- This condition is also known as “Framboesia”. This disease in fact closely resembles syphilis in its pathology.
- This lesion is widespread in Central Africa, Jamaica & Philippines.

**CAUSATIVE ORGANISM:** Treponema Pertene.

- Morphologically this organism is indistinguishable from Treponema pallidum.

**TRANSMISSION:** Is by direct extra genital contact. It has a high incidence in infancy & childhood.
CLINICAL FEATURES:

- Primary, secondary & tertiary stages occur as in syphilis. Yaws affects principally the skin.
- Mucous membrane are usually spared but for the mucocutaneous junctions.
- Nasal lesions are very rare & do not differ in appearance from that of syphilis.
- Advance nasal lesions are associated with extensive destruction of the nose, palate etc.
- Destruction also may involve the whole of the maxilla, face & pharynx.
- In yaws the **serologic tests for syphilis is positive**.
- These lesions characteristically respond to conventional antisyphilitic treatment.

RHINOSCLEROMA (SCLEROMA)

- Name coined by Von Hebra, hence called **HEBRA NOSE**.
- **Respiratory Scleroma or Rhinoscleroma** is a progressive granulomatous disease commencing in the nose & later extending into the nasopharynx & oropharynx, the larynx & sometimes the trachea & bronchi.
- **Laryngeal involvement may occur in almost half the cases** & the disease is perhaps better designated as **Respiratory Scleroma**, rather than Rhinoscleroma.

AETIOLOGY:

- Multifactorial
- Low Socio Economic Status
- Poor Domestic Hygiene
- Overcrowding

ROUTE OF SPREAD:

- Spread by Droplet route.

PATHOLOGY:

- It is caused by gram negative bacilli **Klebsiella Rhinoscleromatis / Frisch Bacilli / Diplo Bacillus**.
- Affects **Any Age** group, with **Female Preponderance**.
- This organism could be a **secondary invader following a viral infection**.
- The organism predominantly resides **intracellularly** & can be difficult to isolate in the laboratory.
- The characteristic histological features include granulomatous tissue infiltrates in the submucosa, characterized by the presence of **plasma cells, lymphocytes & eosinophils**.
- Besides, there are scattered large foam cells (**Mikulicz cells**) which have a central nucleus & a vacuolated cytoplasm containing **Frisch Bacilli & Russel Bodies (modified plasma cells)**.
The Mikulicz cells are transformed macrophages which have ingested the bacillus, but the bacillus being resistant to digestion by the macrophage persists intracellularly. The Russel Bodies resemble plasma cells with an Eccentric Nucleus & Deep Eosin Staining Cytoplasm. Histochemical studies have indicated a high content of mucopolysaccharides around the walls of the bacillus & it is hypothesized that this may be responsible for the protection afforded to the organism from antibiotics & the hosts antibodies.

**CLINICAL FEATURES:**

- There is subdermal infiltration in case of rhinoscleroma
- Three Stages:

1. **The Atrophic Stage:**

   The features resemble that of atrophic rhinitis, including crust formation & a foul smelling discharge (Carpenter's Glue).

2. **Granulomatous or Proliferative (Or Nodular) Stage:**

   - Nonulcerative nodules develop which are at first bluish red & rubbery & later become paler & indurated.
   - These nodules never break down but fibrose & progressively decrease in size. Regional lymph node involvement is extremely infrequent.

3. **Cicatrizing Stage:**

   - Adhesions & stenosis distort the normal anatomy. The disease may extend to involve the lacrimal sac, maxillary sinus, nasopharynx, hard palate, trachea & main bronchi.
   - Bone involvement has also been reported.
   - The shape & contour of the nose changes causing a condition known as “Tapir's nose” (woody feeling on palpation of nose also seen in leishmaniasis). Lymphatic spread is uncommon because of extensive fibrous tissue deposition. This deposition blocks the lymphatics. Occasionally, malignant change has been reported.
   - Commonest site affected in nose - Anterior part of septum
   - Commonest presentation - Nasal Obstruction
   - Commonest site in larynx - Sub glottis
   - **Gothic Sign** - because of fibrosis the pharyngeal wall is pulled up & resembles the top of a church.

**COMPLICATIONS:**

1. External nose deformity
2. Vestibular stenosis
3. Cicatrization of soft palate
4. Nasal regurgitation
5. Tracheal stenosis
**DIAGNOSIS:**

- Only in Rhinoscleroma there is circumferential lesion

**LEVIN TEST:**

- This is a complement fixation test, based on the reaction of the patient’s serum with suspensions of K. Rhinoscleromatis.
- High titers of antibodies against K. Rhinoscleromatis has been demonstrated. This indicates humoral immunity to be intact in these patients.
- Diagnosis in the atrophic stage is extremely difficult (usually diagnosed by complement fixation test) & the disease is usually recognized only in the granulomatous or cicatrizing stage.
- MRI in the hypertrophic stage shows a soft tissue mass with mild to marked high signal intensity in both T1 & T2 weighted images.
- The diagnosis may be further aided by a complement fixation test or by microbiological demonstration of the organism, but it is usually established by a biopsy demonstrating the characteristic histological features. Cellular immunity is impaired with preserved humoral immunity.

**Stains**

- *Warthin Starry silver, Giemsa, PAS stain*

**Culture medium**

- *Mac Conkey Agar*

Diagnosis is confirmed by *Biopsy*.

**TREATMENT**

- Though the disease follows a protracted but usually self-limiting course of its own accord ending in the cicatrizing stage, the organism can nevertheless be extremely difficult to eradicate by antimicrobials.
- Bactericidal antibiotics in large doses are given for a minimum of 4 to 6 weeks & are continued until **two consecutive cultures** from biopsy material are proven negative.
- Initial Surgical Debridement prior to chemotherapy is reported to be useful in the granulomatous stage.
- **Streptomycin i.m. 1gm** for 4-6wks
- **Tetracycline 500 mg Q.I.D.** (but the lengthy nature of the treatment can lead to problems With adverse effects & compliance)
- Recent reports have emphasized the good results achieved with oral therapy with **Rifampicin (450mg for a period of 6 weeks)**
- **Cotrimoxazole** i.e. sulpha methoxazole trimethoprim combination, & **Ciprofloxacin**.
- Local application of 2% Acriflavin for a period of 8 weeks has been noted to be both efficacious & nontoxic.
- **Intralesional steroids** have been tried.
**KAILASA REGIME:** Carboxlic acid (0.2ml) + Glacial acetic acid (0.2ml) + Glycerin (0.4ml) + 10 ml distilled water is injected locally as 1 to 2 ml twice weekly at multiple sites of the lesion. Usually 8-10 injections lead to complete regression of granuloma & restoration of normal nasal patency. This mixture causes chemical necrosis of granuloma.

**RIFAMPICIN:**

**Nasal Instillation** – 1 Amp of rifampicin 125mg diluted in 20mL saline solution & 2mL of the solution is applied twice daily locally for a period of 8 weeks.

**Nasal Infiltration** – 1 Amp of rifampicin 125mg infiltrated into granulomas every other day.

**Irradiation:**

- Dose of 3000-3500 Gy over 3 weeks destroys scleroma but, with the currently available antimicrobials, is unlikely to be required. In late cases where disease has been eradicated, further plastic reconstructive surgery may be required. This may be carried out by nasal endoscopy & laser, if appropriate.

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**Actinomycosis:**

- Actinomycosis is an infectious bacterial disease caused by Actinomyces species such as Actinomyces israelii or A. gerencseriae.
- The condition is likely to be polymicrobial aerobic anaerobic infection.
- Actinomycosis occurs **rarely in humans** but rather **frequently in cattle** as a disease called **LUMPY JAW**.
- This name refers to the large abscesses that grow on the head & neck of the infected individual. Cervicofacial disease is caused most commonly secondarily to dental infection, intraoral trauma or manipulation.

**SIGNS & SYMPTOMS:**

- The disease is characterized by the formation of painful abscesses in the mouth. Actinomycosis abscesses grow larger as the disease progresses, often over months.
- In severe cases, they may penetrate the surrounding bone & muscle to the skin, where they break open & leak large amounts of pus, which often contains characteristic granules (Sulphur granules).
- The purulent leakage via the sinus cavities contains "Sulphur granules," not actually Sulphur containing but resembling such particles. These granules contain progeny bacteria.

**DIAGNOSIS:**
Sometimes there is difficulty in making the correct diagnosis. In addition to microbiological examinations (requires anaerobic processing of culture specimens) magnetic resonance imaging & immunological blood analyses may also be helpful.

**TREATMENT:**

**Penicillin** – frequently used to treat actinomycosis.

In cases of penicillin allergy, **Doxycyclin** is used.

Sulfonamides such as **Sulfamethoxazole** may be used as an alternative regimen at a total daily dosage of 2-4 grams. Response to therapy is slow & may take months.

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**FUNGAL CONDITIONS**

**Rhinosporidiosis:**

- This is an uncommon chronic granulomatous infection that affects the nasal mucosa, ocular conjunctiva & other mucosa.

**AETIOLOGICAL AGENT:**

- **Rhinosporidium Seeberi.**
- In tissue, this organism forms characteristic **abundant, large, thick walled sporangium** like structures containing large numbers of **endospores**. It has long been unclear whether this organism is a fungus.
- Source – **Stagnant pools of fresh water**
- Most common in Rural districts, persons bathing in public ponds or working in stagnant water, such as rice fields.
- Age – 15 – 40
- Males affected more than Females.

**CLASSIFICATION:**

**BENIGN:**

- **Nasal** - Septal Mucous Membrane
- **Floor of Nose / Spur**
- **Nasopharyngeal** - Nasopharyngeal surface of soft palate.
- **Mixed** - Nasolacrimal
- **Bizarre** - Conjunctival / Cutaneous
MALIGNANT: - Generalized

**CLINICAL MANIFESTATIONS:**

- The nose is the commonest site of Rhinosporidiosis, being affected in more than 70 percent of cases.
- The fungus causes the production of large sessile or pedunculated lesions that affect one or both nostrils.
- The infection is insidious in onset & the patient remains unaware of its existence until obstruction develops.
- Patient may present with nasal discharge & epistaxis.
- Rhinoscopic examination will reveal leafy, papular or nodular, smooth-surfaced lesions that become pedunculated & acquire a papillomatous or proliferative appearance. The lesions are pink, red or purple in colour, vascular (bleeds on touch) studded with white dots. In most cases the general health of the patient is unimpaired.
- Spontaneous remission is unusual & left untreated, the polyps will continue to enlarge.

**DIAGNOSIS:**

- The diagnosis is established by histopathological examination of tissue sections.
- These contain large, round or oval sporangia up to 350 µm in diameter, with a thick wall & an operculum. The largest sporangia are filled with spores.

**MANAGEMENT OPTIONS:**

- The treatment of choice is surgical excision of lesions, with or without cauterization of base.
- No drug treatment has proved effective.
- Dapsone 50mg BD, 3 months preop & 6 months postop has been tried & said to prevent maturation of sporangia, promotes fibrosis.
- Recurrence is common & patients should be followed up where possible.

**Aspergillosis**

**CAUSATIVE:** Aspergillus fumigatus (90%), Aspergillus Niger, Aspergillus flavus

**GRANULOMATOUS INVASIVE FUNGAL RHINOSINUSITIS:**

- Pain is the main symptom. An asymptomatic period frequently occurs, symptoms appearing only when the orbit or skull base are involved.
- Chronic Headache, Proptosis & Cranial Nerve Deficits have been reported.
- Maxillary Sinus seems to be a major site.

**INVESTIGATIONS**
Nasal endoscopy reveals nasal congestion or polypoid mucosa & sometimes a soft tissue mass covered by a normal or ulcerated mucosa.

Radiological appearances usually show opacification with bone erosion extending to the orbit &/or skull base.

CT scan helps to determine bony extensions/erosions.

Magnetic resonance imaging (MRI) is helpful to confirm the extension in the soft tissue.

Histopathology reveals fungal invasion of the tissue: bone, mucous membrane, vessels.

Mycologic cultures lead to identification of the species & several causative fungal species have been reported.

**TREATMENT:**

Most patients have been treated with a combination of surgery & antifungal chemotherapy (Itraconazole & Amphotericin B).

**Mucormycosis:**

- Mucormycosis is any fungal infection caused by fungi in the order Mucorales.
- Generally, species in the Mucor, Rhizopus, Absidia, & Cunninghamella genera are most often implicated.
- This disease is often characterized by hyphae growing in & around vessels.

**ROWE JONES CLASSIFICATION:**

1. Non invasive
2. Semi invasive
3. Invasive

**TYPES:** (Superficial COPD)

1. Cerebral
2. Ocular
3. Pulmonary
4. Superficial
5. Disseminated

**SIGNS & SYMPTOMS:**

- Mucormycosis frequently involves the sinuses, brain, or lungs as the areas of infection.
- While oral or cerebral Mucormycosis are the most common types of the disease, this infection can also manifest in the gastrointestinal tract, skin, & in other organ systems.
- In rare cases, the maxilla may be affected by Mucormycosis.
- The rich vascularity of maxillofacial areas usually prevents fungal infections, although more virulent fungi, such as those responsible for Mucormycosis, can often overcome this difficulty.
- There are several key signs which point towards Mucormycosis.
- One such sign is fungal **invasion into the vascular network** which results in **thrombosis** & death of surrounding tissue by loss of blood supply.
- If the disease involves the brain then symptoms may include a one-sided headache behind the eyes, facial pain, fevers, nasal stuffiness that progresses to black discharge, & acute sinusitis along with swelling of the eye.
- Affected skin may appear relatively normal during the earliest stages of infection. 
- This skin quickly progresses to an erythemic (reddening, occasionally with edema) stage, before eventually turning black due to necrosis.
- In other forms of Mucormycosis, such as pulmonary, cutaneous, or disseminated Mucormycosis, symptoms may also include dyspnea (difficulty breathing), & persistent cough; in cases of necrosis, symptoms include nausea & vomiting, coughing blood, & abdominal pain.

**DIAGNOSIS:**

- As swabs of tissue or discharge are generally unreliable, the diagnosis of Mucormycosis tends to be established by a biopsy specimen of the involved tissue.

**TREATMENT:**

- **Amphotericin B (0.5 to 1mg/kg)** (which works by damaging the cell walls of the fungi) is usually administered for a further **4–6 weeks** after initial therapy begins to ensure eradication of the infection.
- **Posaconazole** has been shown to be effective against mucormycosis, perhaps more so than amphotericin B, but has not yet replaced it as the standard of care.
- **Liposomal drug** is also available in the market, but this drug is very expensive. (A liposome is an artificially-prepared vesicle composed of a lipid bilayer. The liposome can be used as a vehicle for administration of nutrients & pharmaceutical drugs.)

**NON SPECIFIC INFLAMMATORY GRANULOMATOUS CONDITIONS**

**Sarcoidosis:**

- Sarcoidosis is a systemic condition of unknown etiology which may affect any part of the body, but most frequently involves **lymph nodes**, skin, **lungs**, eyes, liver, spleen & the small bones of the h&s & feet.

**AETIOLOGY:**

- **Unknown**
- **Age & Sex:** 3rd to 5th decade of life.
- **Female:** Male = 2:1 which is higher in those with upper respiratory tract manifestations.
The etiology of sarcoidosis is unknown, but suspicion has fallen on various infective agents, chemicals (including Beryllium & Zirconium), Pine Pollen & even Peanut Dust. (BZPP)

**IMMUNOLOGY:**

1. Type IV delayed hypersensitivity is depressed
2. Cell mediated immunity is normal
3. Type I humeral immunity is normal
4. Total plasma protein levels are raised
5. There is an increase in the amount of circulating immune complexes.

One suggestion for the pathogenesis of sarcoid is that it is a process initiated by an APC i.e. Antigen Presenting Cell, probably an alveolar macrophage. Subsequently, there is an IL-1 & IL-2 driven T-Lymphocyte proliferation. Monocytes are attracted from the blood by monocyte chemotactic factor (IL-8) & held at the site of reaction by macrophage migration inhibition factor. Monocyte activation by IFN-gamma occurs & this stimulates calcitriol production, which in turn causes macrophage fusion to epithelioid cells & granuloma formation. The persistence of the granuloma may be ascribed to continued antigenic stimulation, failure of suppressor-regulating mechanisms &/or abnormalities in the regulation of the cytokine network.

**HISTOLOGY:**

- **Scadding & Mitchell** defined Sarcoidosis as a disease characterized by formation in all of the several affected organs / tissues of epithelioid tubercles, without caseation.
- These granules either resolve on their own or get converted into hyaline fibrous tissue.
- Thus the sarcoid granuloma is characterized by Epithelioid Cells surrounded by Lymphocytes & Fibroblasts but Devoid of Caseation.
- Crystalline or Calcified Inclusion Bodies are sometimes seen, e.g. Schaumann Bodies.

However, the histological picture is not diagnostic & similar granulomas can occur in a number of other conditions including berylliosis & fungal disease.

**CLINICAL FEATURES:**

1. Nasal stuffiness / obstruction
2. Crusting
3. Blood stained discharge
4. Purulent discharge
5. Facial pain
6. Mucoid discharge
7. Anosmia
8. Pulmonary complaints (dyspnea on exertion, cough, chest pain, & hemoptysis)

- **LÖFGREN SYNDROME** (fever, bilateral hilar lymphadenopathy, & polyarthralgias)

- Nasal cavity mucosa has a characteristic granular appearance (i.e. also called as **Strawberry Skin**).
Pale tiny granulomas could be seen studding the nasal mucosa, giving it a strawberry like appearance.

Nasal mucosa in general would be hyperemic. The nasal mucosa becomes very friable leading on to blood stained discharge.

There may also be crusting of the nasal mucosa associated with mucopurulent discharge. The anterior portion of the nasal septum may perforate, especially if traumatized for example during surgery.

So always beware of performing septal surgery in a patient with Sarcoidosis of nose.

The nasal bones may be involved by a process similar to the dactylitis seen in the fingers & patients may present with a soft tissue mass or expansion of the nasal bridge associated with thickening & discolouration of the overlying skin as in classic lupus pernio.

This may respond dramatically to medical treatment.

The paranasal sinuses may also be affected by the process &/or become secondarily infected. As a consequence, facial pain is experienced by one in five patients with nasal sarcoid.

Sense of smell may be affected due to mechanical obstruction of the olfactory cleft by crusting & fibrosis, or due to direct neuropathy.

Adenoid enlargement or lymphoid hyperplasia may lead to middle ear effusion. The soft tissue of the supraglottic larynx may become thickened & increasingly swollen producing dyspnea & change in voice quality.

**DIAGNOSIS:**

Diagnosis usually relies on a combination of Histology, Imaging, Hematology & Clinical Acumen.

The most reliable test, the Kveim, has regrettably been withdrawn in the UK over fears of virus & prion transfer though without any substantive evidence for this.

1. **KVEIM TEST:** This is a skin test which helps in the diagnosis of Sarcoidosis (Something like tuberculin test).

   This test is performed by intradermal injection of a filtered extract of spleen from a patient with sarcoid. Six weeks later a skin biopsy is taken. The test is positive when the histology shows features of Sarcoidosis.

2. **Angiotensin Converting Enzyme** is found to be elevated in patients during acute phase of the disease (83% of cases). But it is also elevated in a number of other conditions such as tuberculosis, leprosy & primary biliary cirrhosis.

3. **ESR levels, Serum Globulin, Serum & Urinary Calcium** Levels are sometimes raised.

4. Full blood count may show mild anemia, leucopenia, thrombocytopenia & eosinophilia, but clearly none of these tests are specific.

5. Other investigations include (chest X-ray, computerized tomography (CT), perfusion studies, Broncho alveolar lavage & gallium-67 scanning)
6. Biopsy of nasal mucosa is only of use if it appears abnormal as random biopsy of macroscopically normal mucosa is usually negative (in 92 percent of cases).

7. Plain X-rays of the nasal bones may show rarefaction or punctate osteolysis in up to a quarter of cases & this, together with soft tissue changes, may be shown by CT scanning.

**TREATMENT:**

- Some patients with limited disease undergo spontaneous remission without specific treatment, though the majority are offered some form of systemic therapy.
- This consists of a combination of Oral **Steroids, Methotrexate & Hydroxychloroquine**, depending on the severity of the disease.
- Topical treatment may be offered for nasal symptoms including **Intranasal Steroids**, either sprays or drops, glucose & glycerin drops & various forms of nasal douching & irrigation.
- Nasal symptoms may also be helped by the systemic medication. Surgery generally is contraindicated for both cosmetic or functional indications, particularly in the presence of active disease, though endoscopic sinus surgery can be undertaken for secondary bacterial infection with success in selected cases.

**Wegner’s Granulomatosis:**

- Classically Pulmonary, Renal, & Head & Neck Manifestations with Skin Involvement.
- Nose & paranasal sinuses most commonly affected site in the head & neck.

**PATHOLOGY:**

- **Necrotizing vasculitis** affecting small to medium sized vessels (e.g. capillaries, venules, arterioles & arteries) with **Necrotizing Glomerulonephritis**, is common.
- The pathological hallmark is the coexistence of vasculitis & granulomas & classically involves a **triad of airway, lung & renal disease**.

**AETIOLOGY:**

- Unknown
- Age – 15 – 70 yrs.
- Sex – Males and Females equal affection
- It could represent some form of hypersensitivity reaction to an unknown stimulus. The stimulus could be a form of inhaled bacteria. This could explain the frequency with which the respiratory tract is involved.
- The deposition of the immune complexes is thought to be responsible for vasculitis in other conditions, but these have only been demonstrated in a small proportion of patients with Wegener’s granulomatosis.

**IMMUNOLOGY:**
Antibodies reacting with the cytoplasm of granulocytes & Monocytes have been demonstrated by Van Der Woude.

Two main forms of anti-nuclear cytoplasmic antibodies have been demonstrated. Perinuclear (pANCA) & cytoplasmic (cANCA).

**CLINICAL FEATURES:**

- Although the condition is characterized by necrotizing granulomas with vasculitis of the upper & lower respiratory tracts & in the focal necrotizing glomerulonephritis, any part of the body may be affected & in the active cases this involvement may be widespread at the onset.
- **Nose & Sinuses** are involved in more than 80% of cases.
- There may be intra nasal destruction of bone & cartilage leading to collapse of nasal bridge.
- Rapid diagnosis remains of great importance since a fulminating course with a fatal outcome can occur in as little as 48 hours.
- Nasal symptoms include purulent or blood stained nasal discharge, crusting, granulation & can even lead to septal perforations.
- Removal of crusts leaves friable mucosa.
- Minor nasal surgery &/or repeated biopsies during this period may add to the problem.
- In addition, many patients may complain of significant facial pain
- There can be destruction of the eye, orbit, palate, oral cavity, oropharynx & sometimes middle ear.

**ORAL SYMPTOMS:**

- A wide variety of oral lesions have been described, the most common being a hyperplastic granular lesion of the gingiva beginning in the area of the interdental papillae. If a tooth is lost, the socket may fail to heal. Extensive ulcerative stomatitis has also been reported.

**OTOLOGICAL SYMPTOMS:**

- Patients may develop AOM or OME.
- There may be deafness, pain & suppuration.
- Facial nerve paralysis has also been recorded.
- Both Conductive & Sensorineural Hearing Loss occur & while otitis media with effusion may be secondary to inflammatory changes within the nasal cavity
- Wegener's granulomatosis of the temporal bone with necrotizing granulation tissue filling the tympanic cavity has been documented.

**LARYNGEAL & TRACHEAL SYMPTOMS:**

- Laryngeal involvement is unusual, but when present the subglottis & upper trachea are most commonly affected.
- This may present a serious problem with laryngotracheal obstruction.
- Biopsies frequently show only nonspecific changes & are contraindicated leading to further inflammation & scarring.
- Localized disease with a positive c-ANCA test has been well documented & requires ruling out, particularly in an adult presenting with an apparently idiopathic subglottic stenosis.
Extensive laser resection of subglottic stenosis caused by Wegener's is frequently not only unsuccessful, but also causes further stenosis. Gentle dilation, occasional soft internal stenting & localized steroid injection are advised.

**DIAGNOSIS:**

1. The cANCA test is positive in 95 percent of patients with generalized active disease.
2. ESR is found to be elevated
3. Serum angiotensin enzyme levels are increased
4. Presence of vasculitis
5. Granulomas are of epithelioid cell type
6. Multinucleated giant cells have also been demonstrated.

**ACR CRITERIA FOR DIAGNOSIS OF WEGNER'S GRANULOMATOSIS:**

- Nasal, Oral inflammation: Development of painful/painless oral ulcers, purulent or Bloody nasal discharge.
- Abnormal X-ray chest: Shows presence of Nodules, Infiltrates & Cavities.
- Urinary Sediment: Micro Hematuria
- Biopsy: Granulomatous inflammation within the wall of an artery.

**TREATMENT:**

The following drugs can be used in combination.

1. **Steroids** — Prednisolone 60 – 80mg/day
2. **Cyclophosphamide** — 2mg/kg/day
3. **Azathioprine** — instead of Cyclophosphamide in doses of 200mg /day.

**Neoplastic Conditions:**

**Non Healing Midline Granuloma:**
Also known as **Stewart's granuloma**, Midline lethal granuloma, Polymorphic Reticulosus & **Sinonasal Lymphoma**, T / NK cell lymphoma.

- This tumor is responsible for the classical destruction of the midface.
- In the past, death resulted from intercurrent infection of disseminated lymphoma due to a failure of diagnosis or insufficiently aggressive oncologic treatment.
- Recently, similar appearances of aggressive mid facial destruction caused by **Cocaine Abuse** have been reported in which tests for granulomatous diseases & lymphoma have been negative.

**CLASSIFICATION:**

1. **Generalized** lymphoma involving the Sino Nasal Tract
2. Lymphomas of Waldayer’s ring extending to the nasopharynx
3. **Peripheral** – Sinonasal lymphoma the classic T cell lymphoma

**Age & Sex:**

- 1st – 9th decade though the median is 5th – 6th decades.
- Male preponderance has been documented.

**CLINICAL FEATURES:**

- This disorder is associated with aggressive destruction of middle of face. This disease has classically been divided into three stages:

**PRODROMAL STAGE:** Nasal Obstruction & Rhinorrhea. May last few years.

**ACTIVE STAGE:** Areas of necrosis develop in & around the nasal cavity associated with purulent nasal discharge, crusting & tissue loss. There is also progressive destruction of the nasal framework, palate, upper lip extending in to the pharynx. Orbit & skull base also could be involved.

**TERMINAL STAGE:** This stage is characterized by gross mutilation of the face, exhaustion & eventual death. Systemic metastasis is also seen in this stage

**HISTOPATHOLOGY:**

- Biopsy material from tissue beneath the slough & crust. Nasal T cell lymphoma presents a diagnostic problem.
- Atypical cell infiltrates are found dispersed in necrotic areas.
- **Immuno Histochemistry** using a panel of monoclonal antibodies against T cell differentiation antigen should be applied as 80% of peripheral T cell lymphomas show aberrant phenotypes.
- Histologically, the infiltrates are **Polymorphic & Atypical T lymphocytes**
- **Thrombosis & necrosis** are common findings.
- Granulomas & giant cells are **NOT** present in this condition.
An association with **Epstein - Barr virus** has been reported & may be of help in the early differential diagnosis of the condition.

**TREATMENT:**

- Radical full course radiotherapy of 55 Gy or more with wide field coverage including the nose, sinuses & palate.
- Low-dose radiotherapy produced a dramatic response, but no long-term cures.
- Recurrence or development of disseminated lymphoma worsens the prognosis & chemotherapy may be advocated in those lesions classified as high grade.