9. Relapsing polychondritis-presentation, H&N manifestations, diagnosis and treatment. CB- emedicine source

There are 3 diagnostic criteria schemes for this condition, all modifications on the first, McAdam criteria.

**McAdam et al criteria (3 of 6 clinical features necessary for diagnosis)**

- Bilateral auricular chondritis
- Nonerosive seronegative inflammatory polyarthritis
- Nasal chondritis
- Ocular inflammation
- Respiratory tract chondritis
- Audiovestibular damage

**Damiani and Levine criteria (1 of 3 conditions necessary for diagnosis)**

- Three McAdam et al criteria
- One McAdam et al criterion plus positive histology results
- Two McAdam et al criteria plus therapeutic response to corticosteroid or dapsone therapy

**Michet et al criteria (1 of 2 conditions necessary for diagnosis)**

- Proven inflammation in 2 of 3 of the auricular, nasal, or laryngotracheal cartilages
- Proven inflammation in 1 of 3 of the auricular, nasal, or laryngotracheal cartilages plus 2 other signs including ocular inflammation, vestibular dysfunction, seronegative inflammatory arthritis, and hearing loss

Signs and symptoms of relapsing polychondritis include the following:

- **Auricular chondritis**
  - Of patients with relapsing polychondritis, 85%-95% develop auricular chondritis.
  - Unilateral or bilateral auricular pain, swelling, and redness develop suddenly but spare the lobules.
  - The pain and redness usually resolve within 2-4 weeks but may recur.
  - The ear cartilage softens and collapses forward. The external auditory canal can collapse after 1 or more episodes.
  - Nodularity of the auricle may develop.
  - Calcification occurs in 40% of patients.

- **Nonerosive seronegative inflammatory polyarthritis**
  - A seronegative nonnodular arthritis develops in 52%-85% of patients. The acute onset of an inflamed joint may mimic a crystal arthropathy.
  - Most commonly, the arthritis is asymmetric, oligoarticular or polyarticular, nondeforming, and nonerosive. One case of arthritis mutilans has been reported.[23]
  - The ankles, elbow, wrists, proximal interphalangeal joints, metacarpophalangeal joints, and metatarsophalangeal joints are often involved, although any joint may be affected.
  - The costochondral, sternoclavicular, and sternomanubrial joints may be involved.
  - The forefeet are usually spared.
- Effusions may accompany arthritis and may be noninflammatory or mildly inflammatory.

**Nasal chondritis**
- Nasal chondritis occurs in 48%-72% of patients with relapsing polychondritis.
- The nasal chondritis is acute and painful and accompanied by a feeling of fullness over the nasal bridge.
- Mild epistaxis may be present.
- A saddle-nose deformity may develop in longstanding disease.

**Ocular inflammation**
- Collagen types II, IX, and XI are found in the cornea and sclera. Autoantibodies to these collagens, which are found in patients with relapsing polychondritis, may be responsible for direct harm to the eyes.
- Of patients with relapsing polychondritis, 50%-65% develop ocular sequelae related to episodic inflammation of the uveal tract, conjunctivae, sclerae, and/or corneas.
- The most common conditions are episcleritis (39%) and scleritis (14%).
- Eyelid edema, iritis, and retinopathy are found in 9% of patients, and 5% of patients have ocular muscle paresis or optic neuritis.
- Peripheral ulcerative keratitis is found in 4% of patients and has been associated with perforation, endophthalmitis, and bilateral enucleation.
- Papilledema, visual field defects, ptosis, lid retraction, proptosis, and cataracts may also be found on examination.

**Respiratory tract chondritis**
- Respiratory tract involvement affects 40%-56% of patients with relapsing polychondritis and may involve any portion of the respiratory tree, including the distal bronchi.
- Tenderness to palpation may occur over the anterior trachea or thyroid cartilage.
- Chondritis weakens the tracheal cartilage rings, resulting in wheezing, dyspnea, cough, and hoarseness.
- The upper airways can eventually become stenosed and are replaced by collapsible fibrotic tissue. Airways superior to the thoracic inlet collapse upon inspiration, and airways below the thoracic inlet collapse upon expiration; therefore, both inspiratory stridor and expiratory wheezing may be noted on auscultation.
- Inflammation and swelling of the glottis, larynx, and subglottic tissues may require tracheostomy.
- Acute inflammation of the distal airways can lead to obstruction and recurrent pneumonia.

**Audiovestibular damage**
- Audiovestibular derangements are experienced by 46%-50% of patients, usually those with concomitant auricular chondritis.
- Sudden loss of hearing is usually permanent, while tinnitus, nausea, vomiting, nystagmus, and vertigo may subside. In some patients, hearing loss is attributed to vasculitic damage to the eighth cranial nerve.

**Cardiovascular disease**
- Relapsing polychondritis has been reported to affect the cardiovascular system in 24% of patients.
- Aortic and mitral valve regurgitation, aortic aneurysm, aortitis, aortic thrombosis, pericarditis, first- to third-degree heart block, and myocardial infarction, at times mediated through ostial stenosis of a coronary artery or arteries, have been reported.
• Relapsing polychondritis aortitis exhibits inflammation in the media, resulting in loss of glycosaminoglycans and elastic tissue.
  - Any region of the aorta and more than one region simultaneously may be affected. In descending order of frequency, they include the ascending aorta, aortic ring, descending thoracic portion, and abdominal aorta, potentially existing silently rupture and death.
  - The most common clinical presentations include aortic arch syndrome, abdominal aortic aneurysm, and aortic regurgitation.
  - The clinical presentation of aortic regurgitation (resulting from ascending aorta involvement) may include left ventricular failure. Aortic regurgitation may result from damage to the aortic cusps or from annular dilatation due to destruction of supporting tissues.

• Skin disease
  - Skin lesions are found in 17%-39% of patients with relapsing polychondritis.
  - Specific lesions are limited to erythema and edema overlying the inflamed cartilaginous structures. See the image below. Severe auricular edema and inflammation. Courtesy of the University of Washington, Division of Dermatology.
  - Various nonspecific skin lesions have been reported.
    - Aphthous ulcers are the most common.
    - Limb nodules, purpura, papules, sterile pustules, superficial phlebitis, livedo reticularis, limb ulceration, and distal necrosis have been reported.
    - Rarer findings include Sweet syndrome, urticarial vasculitis, and Kaposi sarcoma.
    - Some findings likely represent the skin manifestations of the many conditions associated with relapsing polychondritis rather than specific manifestations of relapsing polychondritis itself.
  - Cutaneous vasculitis: The prevalence of biopsy-proven cutaneous (small vessel) leukocytoclastic vasculitis is approximately 10%, while the prevalence of systemic (including skin) medium-to-large vessel vasculitis ranges from 11%-56%. It may appear as in its typical form of palpable purpura or as hemorrhagic bullae, typically on the lower extremities or other dependent areas.
  - Erythema elevatum diutinum: This has been described in 2 patients with relapsing polychondritis.\(^{24,25}\)
  - Cutaneous polyarteritis nodosa: A patient with relapsing polychondritis presented with relapsing painful red nodules from 1-3 cm in size, occurring on the entire skin and accompanied by arthralgias and myalgias.
  - Other cutaneous lesions reported in patients with relapsing polychondritis and vasculitis included the following:
    - Palpable purpura
    - Acute febrile neutrophilic dermatosis (Sweet syndrome)
    - Subcutaneous inflammatory nodules resembling erythema nodosum
    - Localized ulcerating neutrophilic conditions resembling pustules, furuncles, abscesses, and ulcerating abscesses
  - Panniculitis: This is characterized by 5- to 10-cm tender erythematous nodules showing septal and lobular inflammation.\(^{26}\)
  - Other skin conditions: Isolated case reports of other cutaneous manifestations of relapsing polychondritis include the following:
    - Hyperpigmentation
    - Pustular psoriasis
- Macular purpura of the palms, soles, lower limbs, and buttocks
- Erythematous papular plaques of the face, upper and lower extremities, and thorax
- Alopecia universalis
- Actinic granulomas
- Urticaria
- Angioedema
- Livedo reticularis
- Erythema multiforme
  - Mouth and genital ulcers with inflamed cartilage (MAGIC syndrome): MAGIC syndrome is characterized by an overlap of relapsing polychondritis with Behçet disease. Firestein et al proposed this condition in 1985 in a report of 5 patients.[27] The two types of MAGIC syndrome are as follows.[28]
    - The more common type begins with the oral and genital ulcers of Behçet disease.
    - The second, less common, type is the polychondritis type, in which genital ulcers or erythema nodosum follows the initial presentation of oral ulcers and polychondritis.
- Central nervous system
  - CNS manifestations of relapsing polychondritis are rare and can vary.
  - It is believed that vasculitis of the small and/or medium sized arteries is the underlying etiology.[29] Neurologic symptoms may present before other more frequent manifestations of relapsing polychondritis.
  - Patients may present with seizures, memory loss, delusions, limb weakness, paresthesias or gait disturbances, or other cerebellar symptoms.
  - Cranial nerve damage is common in relapsing polychondritis-associated CNS vasculitis and most often affects the second cranial nerve, followed less commonly by the sixth, seventh, and eighth cranial nerves.
  - Limbic encephalitis has been reported associated with relapsing polychondritis.[30, 31]
  - Aseptic meningitis has been reported infrequently in relapsing polychondritis.[32]
  - Clinical neurologic assessment is an important aspect of the physical examination of patients with relapsing polychondritis.
- Renal
  - From 1943-1980, 129 patients with relapsing polychondritis were seen at the Mayo Clinic, of whom 29 (22%) had evidence of glomerulonephritis based on a diagnostic renal biopsy or the presence of microhematuria and proteinuria.[33]
  - Patients with renal damage are older and more likely to have extrarenal vasculitis and arthritis.
  - A proposed mechanism in the pathogenesis of renal involvement in relapsing polychondritis derives from the deposition of immune complexes leading to glomerular damage.[33]
  - Pathological biopsy findings include segmental necrotizing glomerulonephritis with or without crescents, interstitial lymphocytic infiltrates, interstitial fibrosis, active tubulitis, and glomerulosclerosis.
  - The response to treatment varies from stabilization of renal function to renal failure.

Treatment is systemic CS. 20-60mg in the acute phase and tapered to 5-25mg/d for maintenance.
Dapsone has been tried with some success to control symptoms (25-200mg/d)azathioprine, MTX, cyclophosphamide and cyclosporin A have been tried and are often tried to decrease corticosteroid requirements. NSAIDs not effective. There are no good biologics yet for this condition. There are case reports of anti TNF inhibitors, infliximab, entarcept, adalimumab. Anakinra (IL-1 R antagonist) and leflunomide (inhibits pyrimidine synthesis) and rituximab (anti-CD20 chimeric ab) have shown some benefit.

Surgery is reserved for correction of saddle nose deformity or for tracheostomy, tracheal stent placement, AA repair, cardiac valve replacement.

10. Discuss otorhinolaryngologic manifestations of Wegener’s Granulomatosis, diagnosis and treatment. 
CB Baileys

1:100,000 per year vasculitis. Triad of upper and lower respiratory granulomas, vasculitis, glomerulonephritis.

Other than pneumonitis (most comm. presentation 95%), chronic sinusitis (90%), mucosal ulceration of nasopharynx (75%) and renal disease (80%) are the most common manifestations.

H&N manifestations:

Nasal: crusting, epistaxis, rhinorrhea followed by septal cartilage erosion and saddle nose deformity, as well as nasal stenosis. Staph a is the most common bact pathogen

Oral cavity: gingival hyperplasia/gingivitis

Larynx(25% of pts) edema and ulceration as well as 23% with progressive subglottic stenosis.

Otologic: (20-25%) CHL secondary to SOM, suppurative OM with or without granulation tissue in the middle ear often profound and bilateral, pinna changes often resemble polychondritis.

DX: clinical features, multiple bx (often non-diagnostic so multiple are often done) and serologic studies c-ANCA, PR3, ESR (follows dz progression), signs of glomerulonephritis.

Tx: if left untreated it is fatal in 2 years in 93% of pts. CS and low-dose cyclophosphamide. Azathioprine and MTX are the alternatives to cyclophosphamide.

Review of these agents:

1) cyclophosphamide is a nitrogen mustard alkylating agent which works as chemotherapeutic agent in lymphoma for blocking rapidly dividing cells. In AI diseases, it decreases the bodies immune response. With this agent remember that the bi-product Acrolein causes hemorrhagic cystitis which is prevented using aggressive hydration and mesna.

2) MTX: antimetabolite and antifolate drug, allosterically inhibits dihydrofolate reductase (DHFR), an enzyme that participates in the tetrahydrofolate synthesis. The affinity of methotrexate for DHFR is about one thousand-fold that of folate. DHFR catalyses the conversion of dihydrofolate to the active tetrahydrofolate. Folic acid is needed for the de novo synthesis of the nucleoside thymidine, required for DNA synthesis. Also, folate is needed for purine base synthesis, so all purine synthesis will be inhibited. Methotrexate, therefore, inhibits the synthesis of DNA, RNA, thymidylates, and proteins. For the treatment of rheumatoid arthritis and AI disease, inhibition of DHFR is not
thought to be the main mechanism, but rather the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine, or the inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells. In these cases, patients should supplement their diets with folate.

3) Azathioprine acts as a pro-drug for mercaptopurine, inhibiting an enzyme that is required for the synthesis of DNA. Thus it most strongly affects proliferating cells, such as the T cells and B cells of the immune system. Black box warning that it increases the risk of hepatosplenic T cell lymphoma, particularly in pts with IBD.

12. Discuss the different types of cartilage. Relapsing polychondritis effects which kind of cartilage? CB

There are three major types of cartilage in the body: 1) hyaline cartilage, 2) fibrocartilage, and 3) elastic cartilage. Elastic cartilage exists in the epiglottis and the eustachian tube. Fibrocartilage, as we saw in the section on fracture fixation, often exists temporarily at fracture sites. However, fibrocartilage is permanently present in three major locations in the body: 1) the intervertebral disks of the spine, 2) as a covering of the mandibular condyle in the temporomandibular joint, and 3) in the meniscus of the knee. The third type of cartilage, hyaline cartilage, is most prominently found in diarthroidal joints covering long bones. In addition, hyaline cartilage forms the growth plate by which long bones grow during childhood.

So far, 28 types of collagen have been identified and described. The five most common types are:

- Collagen I: skin, tendon, vascular ligature, organs, bone (main component of the organic part of bone)
- Collagen II: cartilage (main component of cartilage)
- Collagen III: reticulate (main component of reticular fibers), commonly found alongside type I.
- Collagen IV: forms bases of cell basement membrane
- Collagen V: cell surfaces, hair and placenta

Relapsing polychondritis most commonly effects elastic cartilage. It is thought to be auto-immune mediated with a genetic association with HLA-DR4. Various studies have demonstrated acartilage specific circulating antibodies to cartilage specific collagen types II, IX, XI in 30-70% of pt with this disease. However anticolalgen type II antibodies are not specific to RPC, but also seen in RA.