Musculoskeletal Syndromes in Malignancy

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- Certain chronic rheumatic diseases have been associated with **an increased risk of the subsequent development of malignancy** (lymphoma in an individual with primary Sjögren's syndrome)

- certain rheumatic diseases are seen more frequently in the presence of an **underlying malignancy** , such as dermatomyositis (DM).

- many of the **medications** used to treat rheumatic diseases modulate the immune system and may be associated directly or indirectly with an increased risk for the development of malignancy.

- In unusual circumstances , musculoskeletal involvement occurs as a **paraneoplastic process**

PARANEOPLASTIC SYNDROMES

- Musculoskeletal syndromes can develop as a manifestation of a PNP process and occasionally can be the **first presentation** of an underlying malignancy.

- **Hematologic malignancies**, **lymphoproliferative disorders**, and **solid tumors** are associated with a wide variety of PNP rheumatic syndromes.

- ✓ Older age at onset
- ✓ prominent constitutional symptoms
- ✓ atypical features of rheumatic disease
- ✓ limited response to glucocorticoids or other conventional therapy

PARANEOPLASTIC SYNDROMES

- Carcinomatous polyarthritis
- Vasculitis
- Mixed cryoglobulinemia
- Panniculitis
- Fasciitis
- Reflex sympathetic dystrophy syndrome

- Erythromelalgia
- Atypical PMR
- digital necrosis
- Remitting seronegative symmetric synovitis with pitting edema
- Multicentric reticulohistiocytosis

- lupus-like syndromes
- Anti-phospholipid antibodies
- Osteogenic osteomalacia
- Sarcoidosis
- Lymphomatoid granulomatosis

Carcinomatous Polyarthritis

- The term carcinomatous polyarthritis is used to describe **the development of arthritis in association with malignancy**, but it is distinct from arthritis associated with metastasis or direct tumor invasion.

- Although it can have various presentations and may mimic the appearance of (RA) or asymptomatic migratory polyarthritis, carcinomatous polyarthritis is more often a **seronegative asymmetric disease** with predominant involvement of the lower extremities and some sparing of the small joints of the hands

- There is no evidence of direct tumor extension or metastasis and no specific identifying histologic or radiographic appearance

Carcinomatous Polyarthritis

- ✓ Close temporal relationship between onset of arthritis and discovery of malignancy
- ✓ late age of onset (older than 50 years)
- ✓ Asymmetric joint involvement
- ✓ Explosive onset
- ✓ Predominant lower extremity involvement with sparing of wrists and small joints of hands

- ✓ Absence of rheumatoid nodules
- ✓ Absence of rheumatoid factor
- ✓ no family history of rheumatoid disease
- ✓ nonspecific histopathologic appearance of synovial lining
- ✓ no periosteal reaction

Carcinomatous Polyarthritis

- Carcinomatous polyarthritis can occur in association with many types of malignancy, but it has been reported most frequently in association with **breast, colon, lung**, and **ovarian** cancers and with **lymphoproliferative disorders**.

- The **underlying pathogenesis** of this process has not been elucidated; however, the arthritic symptoms may be improved with successful treatment of the malignancy.

Vasculitis

- Vasculitis in association with malignancy is **uncommon** and has a reported prevalence of only 8% in patients with a malignancy.
- Up to **5% of patients with cutaneous vasculitis** have an underlying neoplasm.

- The association seems to be significantly higher with **lymphoproliferative** and **myeloproliferative** disorders than with solid tumors, and vasculitis commonly predates the identification of malignancy .

- The vasculitic process usually affects **small vessels** and is **cutaneous** and only rarely involves significant organs.

Vasculitis

- the **persistent antigen stimulation** from the tumor results in T cell activation or immune complex formation and deposition
- In case reports and small series it has been reported that **(ANCA) – and ANCA + vasculitis** is associated with hematologic malignancies.
- **GPA** has been associated with the development of several types of malignancies, including LPD disorders, bladder cancer, and renal cell carcinoma.

Vasculitis

- **Treatment :** Vasculitis associated with underlying malignancy often responds poorly to conventional therapy directed against the vasculitis.

- More recently, in a study of cutaneous small vessel vasculitis associated with solid tumors investigators found a significant response to immunosuppressive therapy directed against the vasculitis, although concurrent treatments for the underlying malignancy were undertaken.

- Treatment often requires the use of **glucocorticoids in addition to therapy directed against the underlying malignancy**

Cryoglobulinema

- Cryoglobulinemia manifests with symptoms of **hyperviscosity** or **vasculitis**.
- Patients often present with fatigue, arthralgia or arthritis, cutaneous vasculitis or purpura, digital ischemia, neuropathy, and visceral organ involvement (renal or pulmonary).
- three types of cryoglobulins have been identified.

• **Type I**:
Monoclonal Ig, either IgG or IgM;

•this type is associated with **LPD**

•**Type II**: Monoclonal IgM directed against polyclonal IgG;

•were initially thought to be **idiopathic** and were known as EMC
•most of these patients have **HCV** (directly involved in the pathogenesis)

•**NHL** may develop in approximately 5% to 8% of patients who have mixed cryoglobulinemia (after 5 to 10 years of the diagnosis)
•The risk of developing NHL among patients with HCV + cryoglobulinemia may be 35 times higher than general population.

•HCV : **other hematologic malignancies**.

Type III: Mixed polyclonal IgG and IgM

•commonly seen with a **variety of illnesses**, including CTD (SLE and RA) and infections.

Panniculitis

- Fasciitis -panniculitis syndrome is characterized by **swelling and induration of the skin** that extends into deeper subcutaneous tissues and is associated with fibrosis and chronic inflammation.
- Patients may experience **arthritis** and **subcutaneous nodules** similar to those seen in people with erythema nodosum.
- The **arthropathy** seems to be secondary to periarticular fat necrosis, can be monarticular or polyarticular, and may mimic RA.
- This syndrome can be **idiopathic** and have a benign course, or it can be **secondary to a variety of infectious, vascular, or traumatic etiologies.**

Panniculitis

- In a few patients, the fasciitispanniculitis syndrome is associated with an underlying malignancy. **Hematologic malignancies** are most often associated with this syndrome and are usually diagnosed concurrently or within the first year. **breast**, **prostate** and **Pancreatic cancer and pancreatitis** also can be associated with this syndrome.

- Subcutaneous panniculitislike **T cell lymphoma** is considered a primary cutaneous T cell lymphoma, with biopsy required to distinguish it from autoimmune panniculitis.

- Patients with cancerassociated fasciitispanniculitis syndrome are predominantly **female** and generally have a **refractory response** to prednisone.

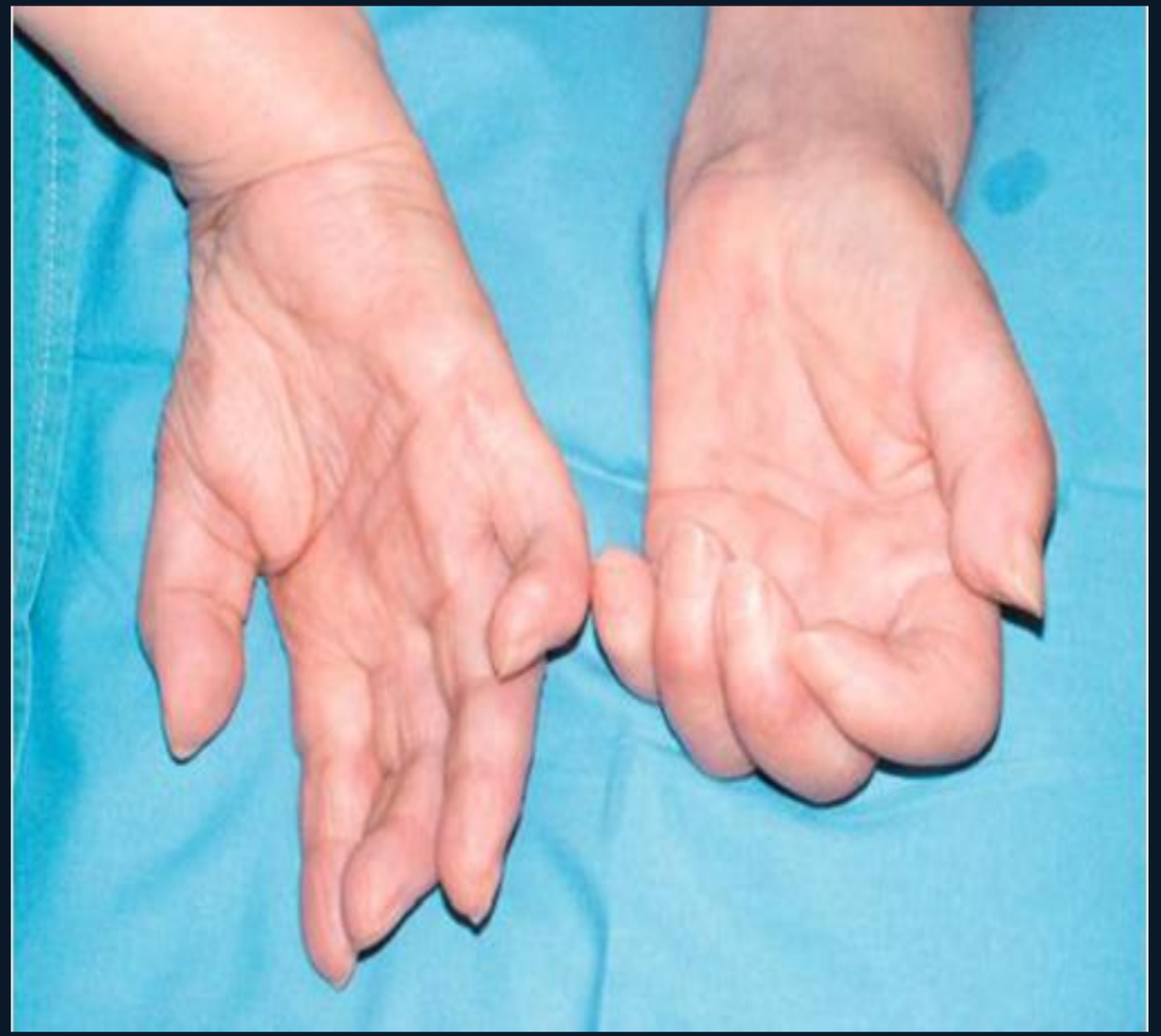
Palmar Fasciitis

- **Palmar fasciitis and arthritis** is a syndrome characterized by :

✓ progressive bilateral contractures of the digits

✓ fibrosis of palmar fascia

✓ inflammatory polyarthritis



Palmar Fasciitis

- The **MTP and PIP** joints are most commonly affected; other affected joints include the elbows, wrists, knees, ankles, and feet.

- Palmar fasciitis is almost uniformly associated with the presence of an **underlying malignancy** (ovarian, breast, gastric, and pancreatic tumors)

- ✓ **severity of manifestations**
- ✓ **bilateral presentation**
- ✓ **strong association with occult malignancy**

Palmar Fasciitis

➢ **Treatment :**

- Neither glucocorticoids nor chemotherapy appear to result in significant improvement

- fasciitis occasionally regresses with treatment of the underlying malignancy.

Reflex Sympathetic Dystrophy

- Reflex sympathetic dystrophy (complex regional pain syndrome), is characterized by:

- ✓ regional pain, swelling
- ✓ vasomotor instability
- ✓ focal osteoporosis in a given limb

- this condition is thought to be caused by **sympathetic dysfunction**

Reflex Sympathetic Dystrophy

- The **absence of associated antecedent factors** such as stroke, myocardial infarction, or trauma and **failure to respond to conventional therapy** may warrant a search for an underlying malignancy.

- **Pancoast tumor** of the lung apices or other malignancies that infitrate the stellate ganglion or brachial plexus have been described in patients with RSDS.

- **Therapy** directed against the underlying malignancy may lead to some amelioration of symptoms

Erythromelalgia

- Erythromelalgia characterized by attacks of severe burning, erythema, and warmth of the extremities, with symptoms predominantly involving the feet.

- Symptoms are often exacerbated when the extremities are placed in a **dependent position, during ambulation**, or **during exposure to increased temperatures**. Partial relief can be obtained through elevation or cooling of the extremity.

- This disorder can occur **idiopathically (60%)** or secondary to another disease (40%).**Myeloproliferative** disorders are common primary causes and have been found to precede the diagnosis of erythromelalgia by several years.

Erythromelalgia

- The underlying pathophysiology of erythromelalgia remains unknown; however, it is often associated with **thrombocythemia**
- The exact cause of the symptoms is unclear, but **microvascular arteriovenous shunting** has been hypothesized.
- The most effective therapy seems to be the use of **daily aspirin**, leading to a significant relief of symptoms.
- Because of the association with MPD routine **monitoring with CBC** is prudent.

Polymyalgia Rheumatica

- **atypical features** of PMR may suggest the presence of occult malignancy :

  - ✓ age younger than 50 years,
  - ✓ limited or asymmetric involvement of typical sites,
  - ✓ ESR less than 40 mm/hour or greater than 100 mm/hour,
  - ✓ severe anemia,
  - ✓ proteinuria,
  - ✓ poor or delayed response to 20 mg of prednisone daily

- **Kidney , lung , and colon cancer and multiple myeloma** are most often found in patients presenting with atypical polymyalgia

Raynaud's Phenomenon and Digital Necrosis

- The development of digital necrosis or profound Raynaud's phenomenon may suggest the presence of :

✓ infection
✓ inflammatory disease
✓ underlying malignancy

- possibility of a paraneoplastic process :

✓ In patients older than 50 years
✓ an asymmetric fashion
✓ association with digital necrosis

Raynaud's Phenomenon and Digital Necrosis

- These features often antedate the diagnosis of the malignancy (**7 to 9 months**).A variety of **solid tumors and LPD** have been associated with this syndrome

- the presence of digital necrosis in patients with **DM** is highly suggestive of the presence of an underlying malignancy.

- **Mechanisms** proposed include :
  - ✓ cryoglobulinemia,
  - ✓ immune complex–induced vasospasm,
  - ✓ hypercoagulability
  - ✓ marantic endocarditis with emboli
  - ✓ necrotizing vasculitis

Remitting Seronegative Symmetric Synovitis with Pitting Edema

- an uncommon disorder primarily affecting the **MCP joints and the wrists**.
- Abrupt onset of arthritis and edema surrounding wrists and small joints of hands

- Although the underlying cause and pathogenesis are unclear, **lymphoma, MDS , and several solid tumors**, mostly adenocarcinoma, all have been reported in association with this illness.

- Characteristics that suggest **possible underlying malignancy** :

✓ presence of **systemic features**, such as fever or weight loss
✓ a **poor response to glucocorticoids**

Multicentric Reticulohistiocytosis

- It is a rare condition characterized by the presence of **cutaneous papules**. The papules are present in the periungual region and on the dorsal aspect of the hands and face.
- This condition is often associated with a **destructive arthritis** of the interphalangeal joints of the hands. Arthritis mutilans may develop in 50% of cases.

- This condition has been reported in association with **hyperlipidemia , autoimmune diseases and malignancies** (25% to 31% of cases)
- The most frequently seen malignancies include carcinoma of the **lung, stomach, breast, cervix, colon, and ovary**

Lupus-like Syndromes

- Lupuslike syndromes are rarely associated with underlying malignancy.
- Isolated case reports have described lupuslike syndromes with **ovarian carcinoma and hairy cell leukemia**.
- Studies of the presence of (**ANAs**) in patients with cancer have yielded mixed results.
- There do not seem to be any **predictive features** that suggest occult malignancy in patients presenting with lupuslike syndromes or positive ANAs.

APS

- More recently, aPLs have been associated with a variety of malignancies.
- Several studies have shown the presence of aPLs in patients with **solid tumors** and **LPD** at a higher frequency than the 1% to 5% seen in the general population.
- however, Correlations between aPLs in individuals with cancer and thromboembolic events have been less clear.

Osteomalacia

- Osteomalacia has been associated with solid tumors and tumors of **mesenchymal origin.**
- Tumors causing oncogenic osteomalacia overproduce (**FGF23**), and elevated serum levels of FGF23 can be detected in patients with this paraneoplastic condition.
- diligent search is indicated in all patients with **late-onset apparent idiopathic osteomalacia**
- **Octreotide scintigraphy** may be a useful tool for identifying occult tumors.
- Upon removal of the tumor, there often seems to be resolution of the osteomalacia and normalization of serum FGF23 levels.

Sarcoidosis

- Granulomas resembling those of sarcoidosis may be found in **lymph nodes that drain sites of malignancy**.
- granuloma formation have been described with many types of malignant lesions, including **lymphomas and solid tumors.**
- Because the clinical and radiographic presentation of sarcoidosis can be virtually indistinguishable from cancer, it is important to pursue **aggressive evaluation** in patients with sarcoidosis.
- The risk of the development of malignancy in patients with established diagnoses of sarcoidosis is controversial.
- Highest incidence of “malignancy” during **first 4 yr after** detection of granulomas

Lymphomatoid Granulomatosis

- This condition is a rare disorder with **angiodestructive** and **lymphoproliferative** features involving the lung and, less often, the skin and CNS.
- **lymphocytic infiltration** of vessels is a hallmark of the disease
- Despite the predominance of **T cells** within inflammatory infiltrates, an **(EBV)-associated B cell proliferation** may underlie the pathogenesis of the disease.
- **Prognosis** is poor (more recent reports suggest some response to rituximab therapy)
- **Frank lymphomas** evolve in 25% of cases.

Inflammatory Myopathies

- The association between inflammatory myopathy and cancer is well described in adults
- the **pathophysiologic mechanisms** underlying the association remain elusive.
- Many epidemiologic studies substantiate this association, which appears stronger for **DM** than for other subtypes.
- Associations between **PM and IBM** are becoming increasingly recognized.

Inflammatory Myopathies

- Zampieri et al. hypothesized that in genetically predisposed patients, cancer is accompanied by **subclinical tumorinduced myopathy**, which can later evolve to full blown autoimmune myositis.

- investigators suggest that **myositis specific antigens** are expressed in regenerating muscle fibers and trigger an aberrant autoimmune response that acts as a positive feedback loop.

- On average, the **prevalence of malignancy** in association with the inflammatory myopathies has been approximately **15% to 25% (**6% to 60% in patients with DM and from 0 to 28% in patients with PM)
- Other estimates have placed the **incidence of cancer** in patients with inflammatory myopathies at **five to seven times** that of the general population.

Inflammatory Myopathies

- **solid tumors** are most often seen in cancerassociated myositis as opposed to lymphoid malignancies.

- **Most common tumor types :**
  - ✓ ovarian, lung, and gastric tumors in **European populations**
  - ✓ nasopharyngeal malignancies in **Asian populations**

- cancers are most commonly diagnosed within **1 to 2 years** of diagnosis of DM.

Inflammatory Myopathies

- In people with **PM**, the relative risk (RR) of developing internal malignancies seems to be lower than that for people with DM, but it is consistently increased compared with that expected in the general population.
- Far less is known about the association of **IBM** and underlying malignancy
- removal of the malignancy may result in improvement of the myopathic process, which further supports the **paraneoplastic nature** of myositis in some cases

Factors That Predict Malignancy in Myositis

- ✓ Age >45 yr
- ✓ Male gender
- ✓ dysphagia
- ✓ Cutaneous necrosis
- ✓ Cutaneous vasculitis
- ✓ Rapid onset of myositis (<4 wk)
- ✓ shawl sign

- ✓ Elevated ESR/CRP
- ✓ Anti–p155-140 (TIF-1 γ) and anti-NXP2 (anti-MJ) antibodies
- ✓ Refractory disease
- ✓ distal extremity weakness,
- ✓ prominent pharyngeal and diaphragmatic involvement

Factors Associated with Reduced Risk of Malignancy

- ✓ ILD
- ✓ arthritis/arthralgia
- ✓ Raynaud's phenomenon
- ✓ Anti-Jo-1
- ✓ Anti-ENA
- ✓ other myositis-specific antibody

Inflammatory Myopathies

- For patients with an inflammatory myopathy a workup for the presence of malignancy should be performed. any workup should be tailored to the individual patient's **age, symptoms, and signs**.
- **imaging of the chest, abdomen, and pelvis** may increase the potential for the discovery of an underlying malignancy.
- Other investigators have suggested the use of **serum tumor markers.**
- a prospective study of **wholebody PET/CT** was found to be comparable with broad conventional screening.

Inflammatory Myopathies

- Malignancies associated with inflammatory myopathies have been known to develop **many years after the diagnosis of muscle disease**, and thus continued vigilance and **repeated screening** for malignancy are warranted.

- **Clinical suggestions** include performing a careful history, physical examination, general laboratory screening, stool heme occult ×3, prostate examination/PSA test in men, and Pap smear, mammogram, gynecological examination, and possibly transvaginal sonography and the CA125 test in women

RISK OF MALIGNANCY IN SYSTEMIC AUTOIMMUNE DISEASES

- The association between rheumatic disease and malignancy is thought to be mediated, at least in part, by **chronic immune stimulation and hyperactivity** that may lead to malignant transformation.

- Other factor : the potential oncogenic properties of many of the immunosuppressive and cytotoxic **medications** prescribed to treat autoimmune diseases.

- **LPD** have developed in patients with rheumatic diseases and in recipients of solid organ transplantations treated with immunosuppressive agents.

- **EBV** has been implicated in the development of lymphoid neoplasia in IS patients.

Sjögren's Syndrome

- **Lymphoproliferative disorders** are complications in approximately 4% to 10% of cases of primary Sjögren's syndrome.
- Most LPD : **NHL** , specifically diffuse large B cell lymphoma, MALT lymphoma, and other marginalzone lymphomas.
- Waldenström's macroglobulinemia, CLL , and multiple myeloma were more rarely reported.
- Generally, the development of lymphoma is a **late manifestation** of Sjögren's syndrome; it often is seen after the disease has been present for 6.5 years.

Sjögren's Syndrome : Predictors of progression to lymphoma

- ✓ palpable purpura,
- ✓ cutaneous ulcerations,
- ✓ cryoglobulinemia
- ✓ low serum complement levels (low C4)
- ✓ monoclonal gammopathies,
- ✓ cytopenias, lymphopenia
- ✓ splenomegaly,
- ✓ adenopathy
- ✓ parotid or salivary enlargement
- ✓ disappearance of RF , decline of IgM
- ✓ elevated levels of serum (Flt3L)
- ✓ evidence of germinal center–like formations in minor salivary gland biopsies

Sjögren's Syndrome

➢ possible mechanisms :

- It is believed that **chronic B cell stimulation** may lead to the malignant transformation of clonal lines characteristic of Sjögren's syndrome.
- The presence of a **viral trigger** accounting for malignant transformation is one possible theory.(EBV)
- It also has been reported that **chromosomal translocations** are present with increased frequency in patients with Sjögren's syndrome in whom lymphoma has developed. (translocations of the protooncogene Bcl2)

Rheumatoid Arthritis

- it has been well established that RA is associated with a twofold to threefold increased risk for the development of **lymphoproliferative disorders**, the magnitude of which has remained constant despite dramatic changes in therapy.

- Many factors, including **chronic inflammation** and immune dysregulation, in addition to potential oncogenic properties of **immunosuppressive therapies** for the treatment of RA, must be considered when evaluating the risk of the development of hematologic malignancies.

- It is often difficult to separate the effects of medication use from the underlying severity of inflammation that makes medication use necessary or indicated

Rheumatoid Arthritis

- In general, lymphomas in patients with RA seem to be predominately **diffuse large B cell type** and favor **non– germinal center subtypes**.
- Most studies have suggested that the risk for the development of lymphoma is related to the **degree of inflammation.**
- No association between any **specific drug** and the development of lymphoma was identified

Rheumatoid Arthritis

➢ Associated Factors :

- ✓ Presence of paraproteinemia
- ✓ Greater disease severity
- ✓ longer disease duration
- ✓ immunosuppression
- ✓ Felty's syndrome

➢ Clinical Alert :

- ✓ Rapidly progressive, refractory flare in long-standing rheumatoid disease may suggest an underlying malignancy

Rheumatoid Arthritis : DMARD

- data from studies when taken together suggest a **possible increased risk for the development of LPD** in patients with RA who are treated with DMARDs.

- However, more recent studies have suggested that this increased risk may be due to the duration and **severity of the underlying disorder** rather than to specific medication use.

- After approximately two decades of use, use of **TNF inhibitors** as a class has not been shown to increase risk of lymphoma above the rates in the general RA population.

Rheumatoid Arthritis : Risk of Solid Tumors

- Despite persuasive evidence of increased risks of LPD associated with underlying RA, rates of **overall allsite malignancies** do not seem to be higher compared with the general population.
- The overall “null” result of all malignancies is due to the combination of an increased risk of LPD offset by an apparent decreased risk of colorectal malignancies.
- The decreased risk of colorectal cancer has been attributed to longterm use of NSAIDs among patients with RA.
- Aside from LPD , only a few solid tumors have been associated with RA, including **lung cancer and skin cancer**

Rheumatoid Arthritis : Risk of Solid Tumors

- An increased risk of **lung cancer** in patients with RA has been seen in multiple studies.
- This association may be related to **tobacco** use, which seems to be a common risk factor for the development of RA, in addition to its wellknown association with lung cancer

Rheumatoid Arthritis : Risk of Solid Tumors

- A slightly increased risk for the development of **nonmelanoma skin cancer** (SCC/BCC) has been noted in several studies
- newer data suggesting an increased rate of **melanoma** among patients with RA.
- A recent metaanalysis has shown that the risks of both melanoma and nonmelanoma skin cancer appear to be further increased by the use of **TNF inh.**
- it is reasonable to suggest **periodic skin examinations** in patients with RA, particularly those who have other risk factors (smoking, increased UV exposure, use of TNF inhibitors).

SLE

- In a multinational cohort study The authors found a slightly increased risk of malignancies overall (SIR, 1.15), with higher risks for the development of **hematologic malignancies** (SIR, 2.75), particularly NHL (SIR, 3.64).
- The incidence of lymphoma in this study appeared to be **early** in the course of SLE.
- Cancer risks in this multinational cohort have recently been updated in 2013 . The SIR for all hematologic malignancies was 3.20, and it was increased to 4.39 for NHL.
- In a casecohort study within the multisite international SLE cohort, **age**, **disease-related damage,** and **smoking** were found to be associated with an increased risk of malignancy; use of immunosuppressant **medications** may contribute to an increased risk of hematologic malignancies.

SLE

- several theories have arisen to explain the possible connection between SLE and malignancy, especially **B cell lymphoma** :

- ✓ **certain immunologic defects** may predispose patients to SLE and B cell lymphoma, including apoptosis dysfunction, chronic antigenic stimulation, and overexpression of the Bcl2 oncogene.

- ✓ Viruses (**EBV** in particular)

- ✓ **elevated levels of APRIL** (A ProliferatingInducing Ligand) has been found in sera and tumor specimens in patients with SLE who have NHL.

SLE

- NHL should be considered in patients with SlE who have adenopathy or masses;
- lymphoma of the spleen is another cause of splenic enlargement in SlE

SLE

- **Cervical cancer** remains an important issue for women with SLE, and an increased risk may come about for different reasons, including :

✓ (1) reduced clearance of HPV

✓ (2) immunosuppressive medications;

✓ (3) reduced rates of routine Pap smears and other screening procedures in patients with chronic illnesses.

- Different studies have implicated increased prevalence of **HPV infection and other STD**
- data have suggested a reduced risk of **hormone sensitive tumors** among patients with SLE, including **breast**, **endometrial**, and possibly ovarian and prostate tumors

SLE

- In several studies, a link has been identified between SLE and the development of **lung cancer**

- in one cohort study, the majority of cases (71%) occurred in smokers, 25% of cases were in men, and few (20%) had previous exposure to immunosuppressive agents.

SLE

- Overall,the presence of SLE carries a risk for the development of cancer,particularly:
  - ✓ **nonHodgkin's lymphoma**
  - ✓ **lung cancer,**
  - ✓ **cervical cancer**
- The underlying causes of these associations are unknown,
- Data also suggest that patients with lupus may be less likely to receive cancer screening..

discoid lupus erythematosus

- **Malignancy :** squamous cell epithelioma

- **Associated Factors :**

  - Found in oldest plaques, ≥20 yr after onset of discoid lesion,
  - primarily in men 30-60 yr old

- **Clinical Alert :**

  - Poorly healing skin lesion within discoid plaques should be evaluated

Systemic Sclerosis

- Estimates of the prevalence of cancer among patients with scleroderma range from **3.6% to 10.7%** . 13% of deaths among patients with SSc are caused by cancer.
- The malignancies that have been implicated are often in organs affected by **inflammation and fibrosis**, including the **lung, breast , esophagus, and skin**.
- There is an apparent increase in the observed number of cases of lung cancers that occur in the setting of pulmonary fibrosis but not in association with tobacco use.
- In one study : A strong association with lung cancer and a significant increased risk for **hematologic neoplasms** was seen.
- associations between Ssc specific **autoantibodies** and the development of cancer (antiRNA polymerase III)

Systemic Sclerosis

- the consequences of **chronic inflammation and fibrotic processes** may damage tissue, cells, and DNA, leading to altered immune responses and the development of malignant transformation, triggering the development of lung cancer or cutaneous malignancies.

- Researchers recently reported **genetic alterations of the POLR3A locus** in six of eight patients with antibodies to **RNA polymerase III** but not in eight patients with scleroderma who had other autoantibody specificities

- Analyses of peripheral blood lymphocytes and serum suggested that **POLR3A mutations triggered cellular immunity and cross reactive humoral immune responses.**

Systemic Sclerosis

- **NHL** : Cases of NHL seem to be more likely to occur within the **first year** of the diagnosis of SSc.
- **nonmelanoma skin cancers , primary liver cancers , and hematopoietic cancers**.
- The greatest risk seems to correspond to areas commonly affected by fibrosis (**lung and skin**)
- **Esophageal involvement**, is the likely cause for an increased incidence of Barrett's esophagus and the development of esophageal cancer

Systemic Sclerosis

- **Annual chest radiograph** after fibrosis is detected
- Change in **skin** features or poorly healing lesions should be evaluated
- **Esophagoscopy** and biopsy, if indicated, of distal esophageal constricting lesions

- **Localized scleroderma**, including morphea or linear scleroderma, does not seem to convey an increased risk of malignancy.

- **Sclerodermatous skin changes** have been reported with breast, ovarian, pulmonary, and GI cancer.

- Several reports have described the development of **post irradiation morphea** in patients treated for breast cancer

Paget's disease

- **Malignancy :** osteogenic sarcoma

- **Associated Factors :**
  - ✓ development of severe pain
  - ✓ increasing incidence with age

- **Clinical Alert :**
  - ✓ swelling and bone destruction in preexisting Paget's disease may be sarcoma; diagnosis may require biopsy

PRIMARY TUMORS AND METASTATIC DISEASE

Primary Musculoskeletal Tumors

- The most common manifestation of Primary malignant bone tumors : **pain** in the area of the lesion, which may be accompanied by a sympathetic **effusion or stiffness in the surrounding joint** . This discomfort does not seem to be activity related and is often worse at night. However, these tumors can manifest as painless masses or as pathologic fractures.

- **Systemic features** are rare with all of these tumors except for Ewing's sarcoma.

- These tumors have their highest incidence in **childhood and adolescence**

- These tumors commonly arise out of areas of rapid growth **(metaphysis near the growth plate)**

Nonosseous Tumors

Multiple myeloma; round cell tumors

Osseous Tumors

Osteosarcoma; chondrosarcoma; giant cell tumors; fibrosarcoma

Primary Bone Tumors

Primary Musculoskeletal Tumors

- **Osteosarcoma** is the most common of the tumors and generally occurs in individuals in the second decade of life or in elderly individuals.

- Osteosarcoma also can occur as a result of **radiation therapy .**

- **Chondrosarcoma** has been reported as the second most common of the malignant bone tumors.

- This tumor may occur as a primary tumor or as a malignant transformation in the setting of benign lesions, such as an enchondroma or osteochondroma

Primary Musculoskeletal Tumors

- **round cell tumors** include primary lymphomas of bone, Ewing's sarcoma, and metastatic neuroblastoma.

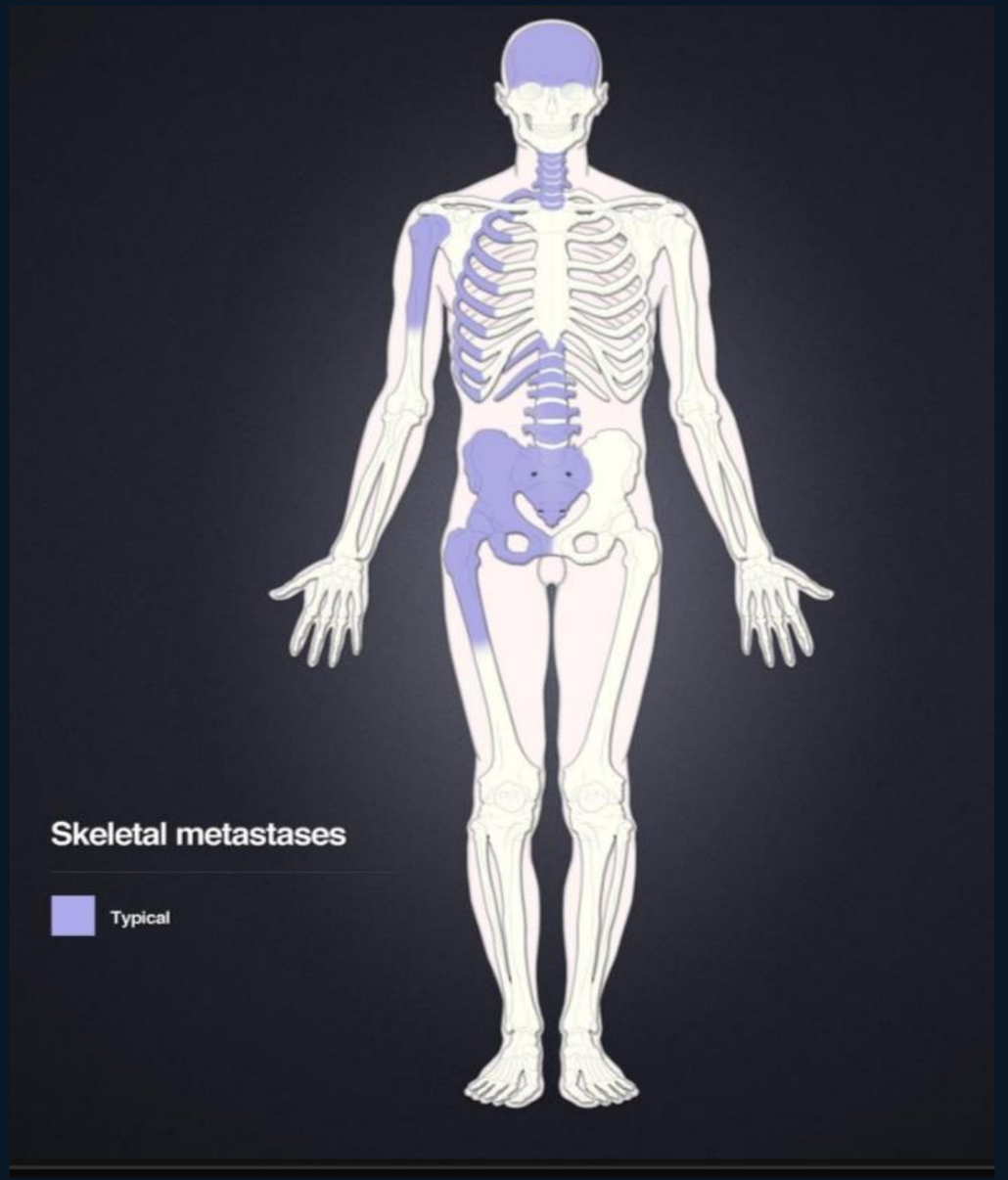
- Ewing's sarcoma is a common primary bone tumor of childhood.

- **Giant cell tumors** as a group account for 4.5% of bone tumors.

- They usually arise from the metaphysis or epiphysis of long bones, generally around the knee.
- Most are benign, but a few are malignant lesions, usually arising out of a previously irradiated benign giant cell tumor.

Metastatic Disease

- most malignant lesions in bone are metastatic. Metastasis rarely affects muscles, joints, or adjacent connective tissue; more commonly, it affects **bone**.
- The most common sites of metastasis are the **spine and pelvis**.
- When **distal or acral metastasis** is identified, it is often associated with lung cancer.
- Primary tumors generally associated with metastases to bone include tumors in the **prostate, thyroid, lung, breast, and kidney**.



Metastatic Disease

- **Arthritis** associated with metastatic carcinoma is most commonly monarticular and usually affects the knee.
- **Metastases to the extremities** can simulate gout, osteomyelitis, tenosynovitis, or acroosteolysis.
- The development of **joint involvement** can be related to direct synovial implantation or involvement of the juxtaarticular or subchondral bone.

Frequent Features of Arthritis Resulting from Metastatic Carcinoma

- ✓ Presence of constitutional symptoms
- ✓ Prior history of malignancy
- ✓ Protracted clinical course
- ✓ negative culture results, negative crystal analysis
- ✓ Medical therapeutic failure
- ✓ Rapid reaccumulation of hemorrhagic non-inflammatory effusion
- ✓ Radiologic evidence of destructive process

Malignancy	Pathogenesis
Leukemia	Infiltration of synovium
Lymphoma	Metastases or invasion of bone, rarely joint
Angioblastic lymphadenopathy	Vasculitis, cryoglobulinemia
Multiple myeloma	Metastasis or invasion of bone, hyperuricemia

Musculoskeletal Manifestations of Hematologic Malignancy

Leukemia

- **Bone pain** is the most common musculoskeletal manifestation and has been reported to occur in 50% of adults with leukemia.
- **Long bone pain** is more common in children, whereas **axial pain** is more common in adults.the bone pain is more common in the lower than in the upper extremities.
- **Overt synovitis** can develop in association with leukemia and can result in the development of monarticular or polyarticular arthritis.
- The **pathogenesis** seems to be leukemic infiltration of the synovium and subperiosteal tissue.

Leukemia

- Most cases of **arthritis** associated with leukemia are seen in children .On average, symptoms of arthritis preceded the diagnosis of leukemia by **3.25 months**.

- The **most common patterns** of presentation were an asymmetric large joint involvement in association with low back pain, followed by symmetric polyarthritis mimicking early RA.

- **Rheumatic manifestations :** morning stiffness, low back pain, nonarticular bone pain, pain out of proportion to objective findings, low grade fever, elevation of the ESR.

Leukemia

- Many of these children had been incorrectly treated for **juvenile RA or osteomyelitis** before the diagnosis of leukemia

- The response to NSAIDs, glucocorticoids, and antirheumatic therapy was reportedly poor, but **chemotherapy** resulted in substantial improvement of the rheumatic manifestations.

Multiple Myeloma

- Multiple myeloma is a a **nonosseous malignant tumor** arising in the marrow.
- In contrast with the other primary tumors of bone, which have their highest incidence in children and adolescents, myeloma is a tumor of **adults**, occurring most commonly in the fifth and sixth decades of life.
- The most common musculoskeletal feature of this disease is the development of **bone pain**. Other hallmark features are **diffuse pain** and **stiffness**

Multiple Myeloma

- The **lytic lesions** , which can occur in any area of the skeleton, are produced by focal accumulations of plasma cells . Osteosclerotic lesions also have been reported.
- **True arthritis** is rare, but cases of arthritis resulting from articular and periarticular invasion with malignant cells have been reported in individuals with multiple myeloma and Waldenström's macroglobulinemia.
- A secondary feature of the disease is the development of **hyperuricemia** and **gout**.
- **Sjögren's syndrome** and other autoimmune phenomena also have been described in association with multiple myeloma.

Lymphoma

- Musculoskeletal symptoms have been reported in **25%** of cases of NHL .
- The most common musculoskeletal problem : **bone pain**
- more than 50% of patients have evidence of bone lesions at **autopsy** . however, few patients actually present with arthritis or bone pain.

- NHL has been reported to manifest as a **seronegative arthritis**.
- Monarticular and polyarticular involvement can occur.
- Cases have been reported of polyarthritis simulating **RA** in the setting of NHL.

- Suspicion of lymphoma should be heightened in patients in whom **severe constitutional symptoms** seem out of proportion to the degree of arthritis, especially in patients who are negative for rheumatoid factor.

Angioimmunoblastic Lymphadenopathy

- it is a rare LPD marked by the clinical features of :
  - ✓ lymphadenopathy
  - ✓ hepatosplenomegaly
  - ✓ rash
  - ✓ hypergammaglobulinemia

- Patients can experience a **nonerosive , symmetric, seronegative polyarthritis** concurrent with other features or as an initial symptom of the disease.

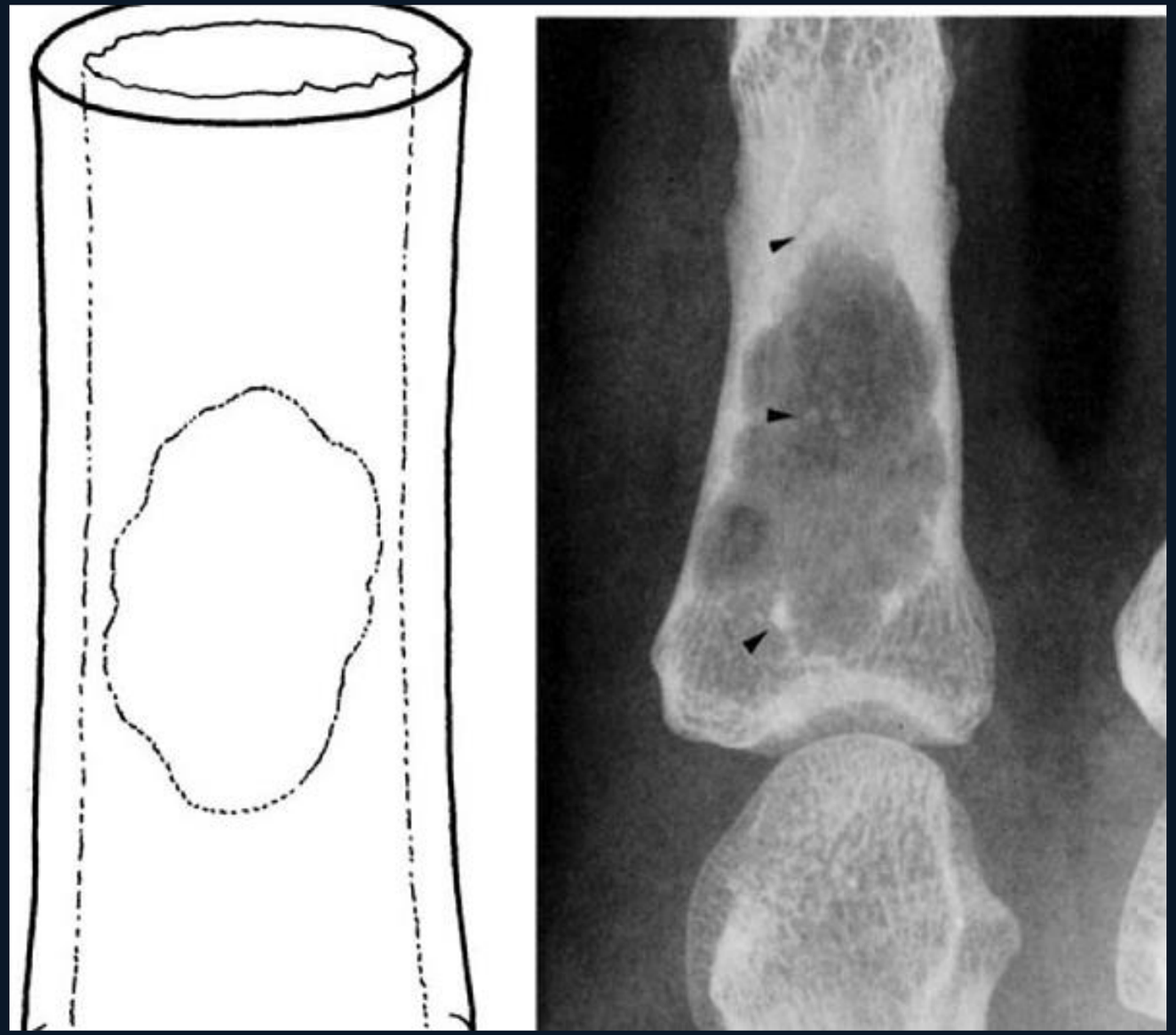
Radiographic features of bone tumors

- Radiographic features of bone tumors can be significant when interpreting the **duration** of disease and the **type** of malignancy.
- Lesions may be lytic or blastic
- **patterns** of destruction often reflect the aggressiveness of tumors

➢ Geographic bone destruction.

- The lesion in the proximal phalanx demonstrates geographic bone destruction, a central location, lobulated margins, and small foci of calcification (arrowheads).

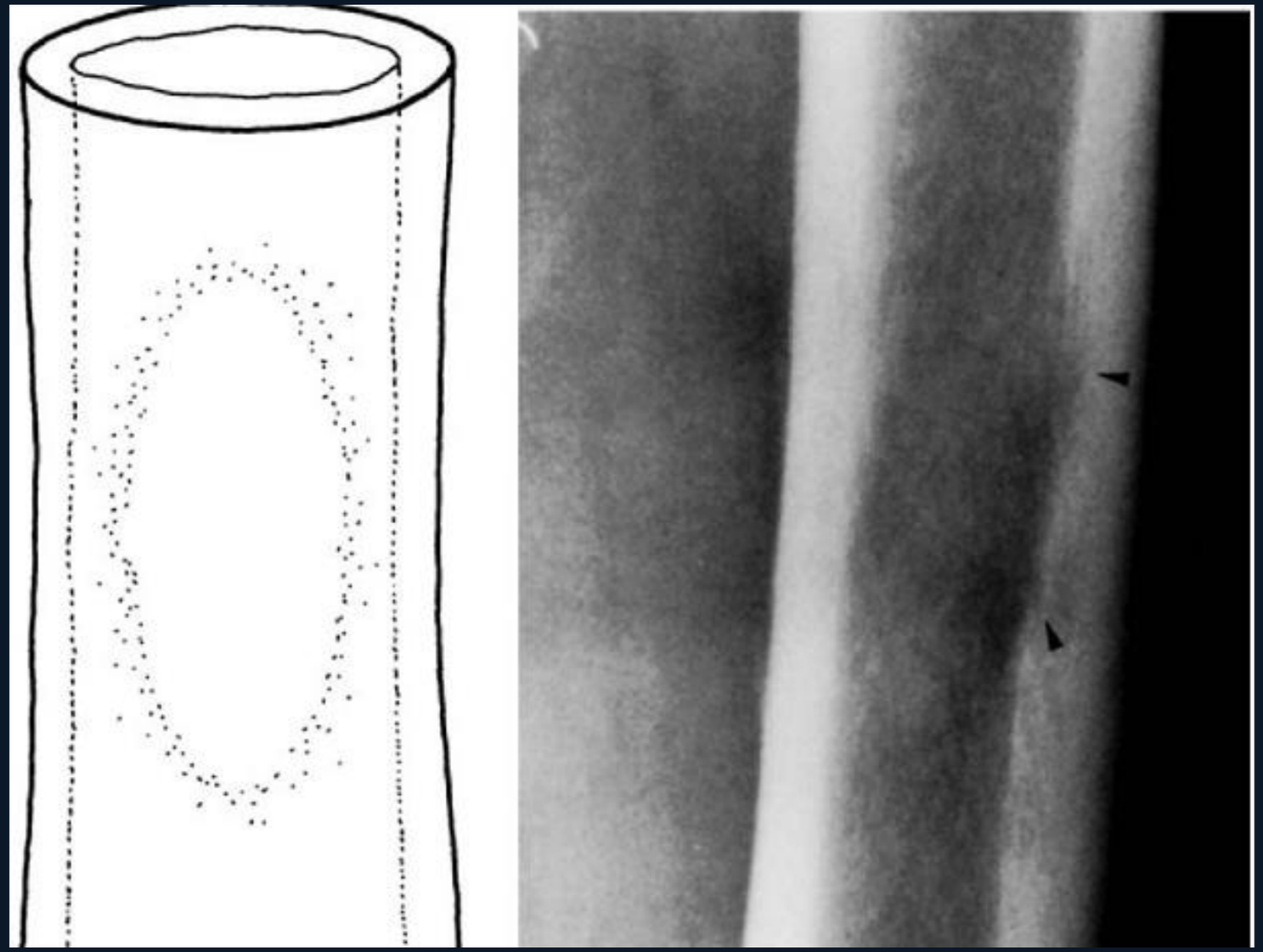
(Final diagnosis, enchondroma)

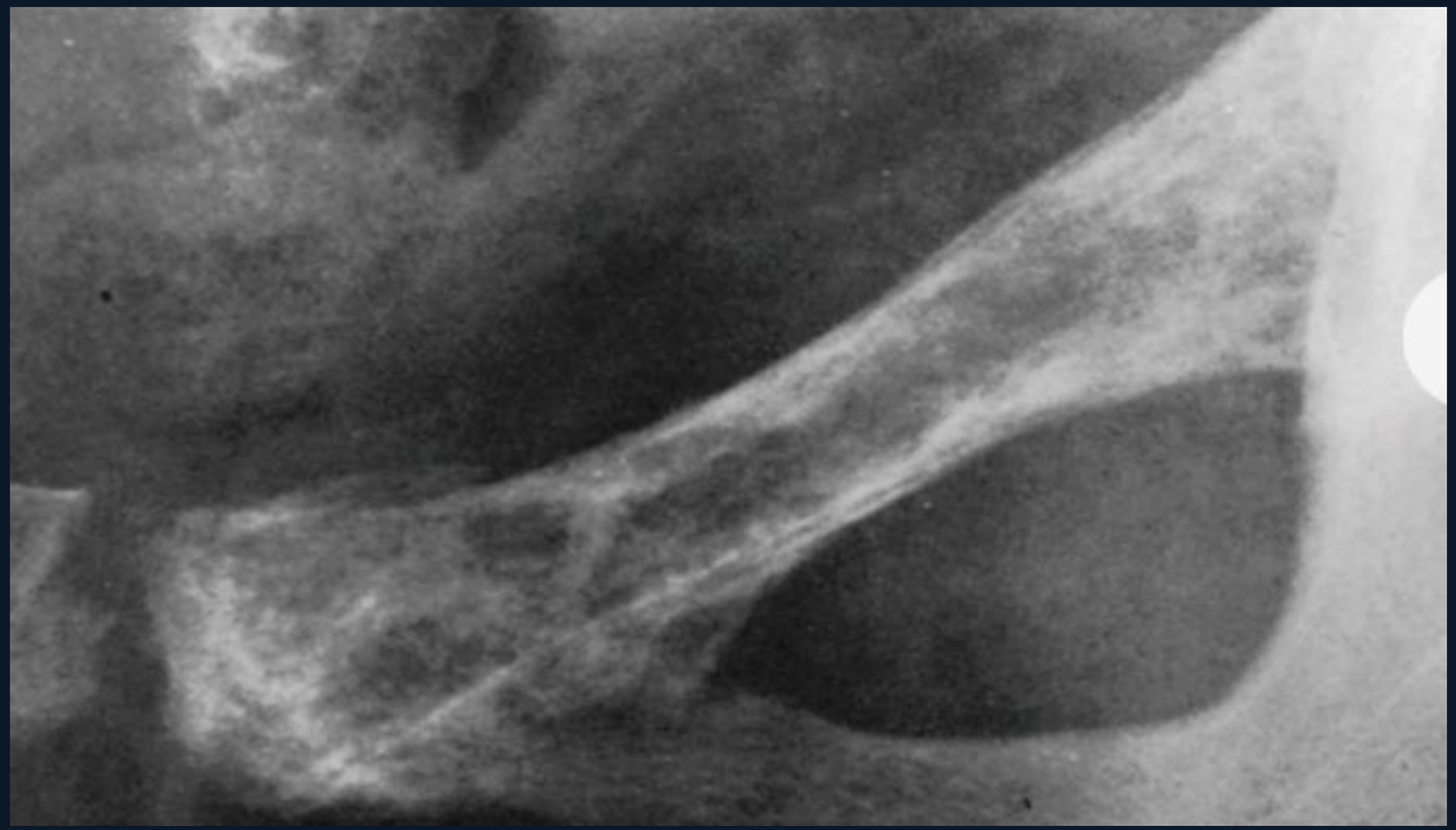


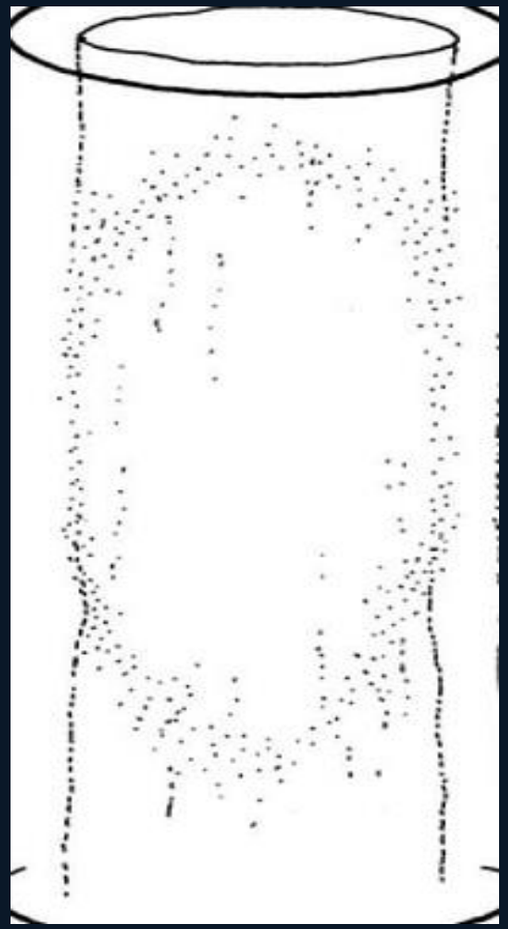
➢ Moth-eaten bone destruction

- A lesion with moth-eaten bone destruction is identified in femur.
- Note its poorly defined margins and erosion of the endosteal margin of the cortex (arrowheads).

(Final diagnosis, lymphoma)







➢ **Permeative bone destruction**.

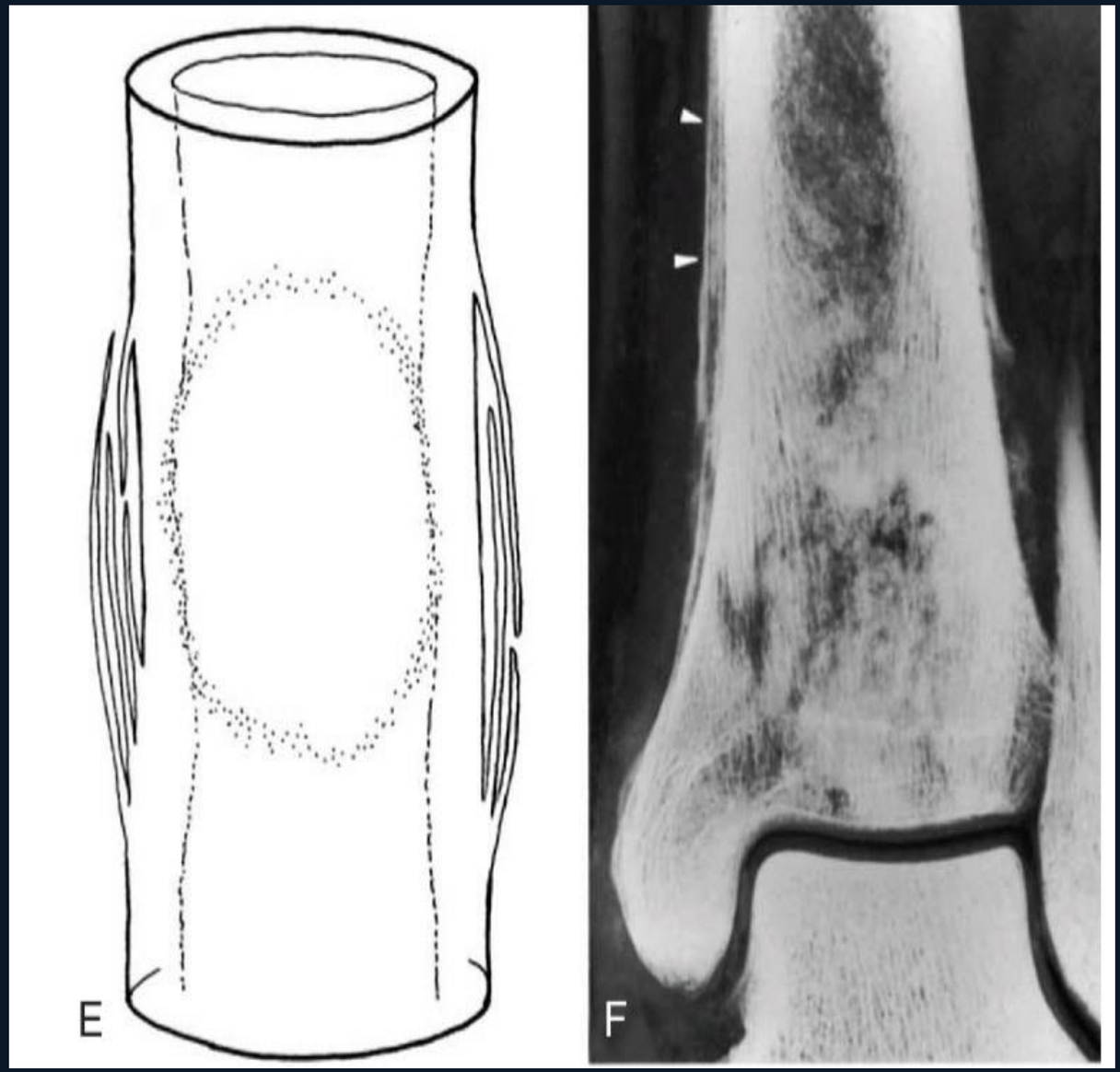
- The lesion in the superior pubic ramus reveals permeative bone destruction with cortical erosion, periostitis, and a soft tissue mass (Final diagnosis, lymphoma)

- Multiple layers of periosteal bone: **onion-skin pattern**.

- The specimen radiograph shows such a pattern along one side of the distal portion of the tibia (arrowheads).

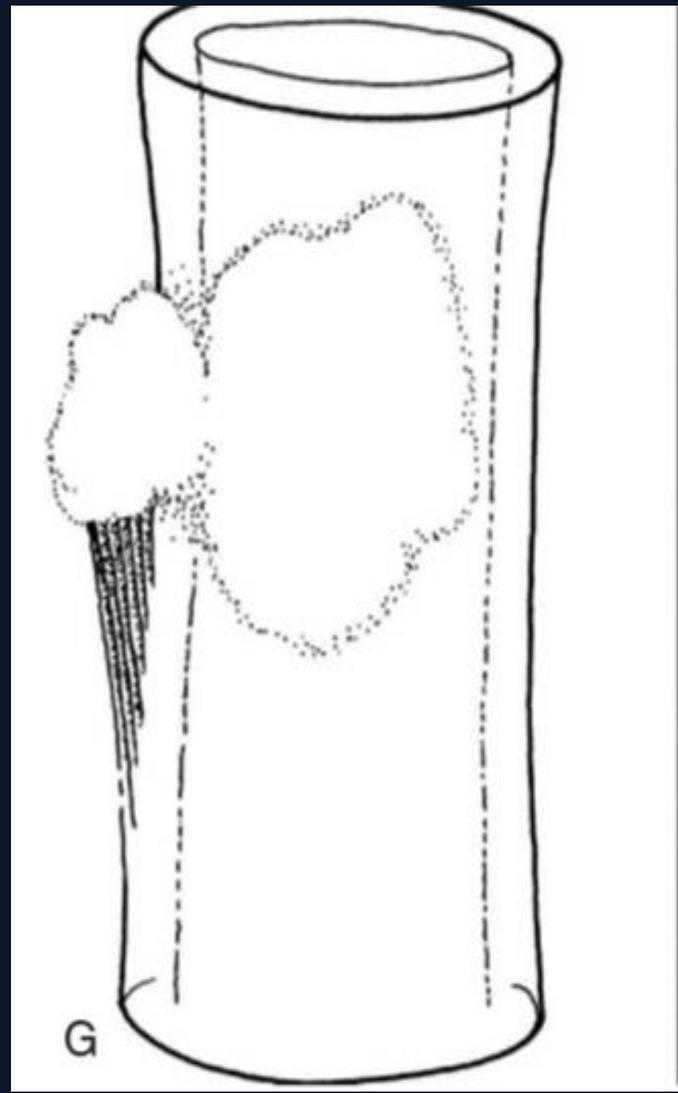
- On the other side of the bone, a more complex pattern of periostitis is seen

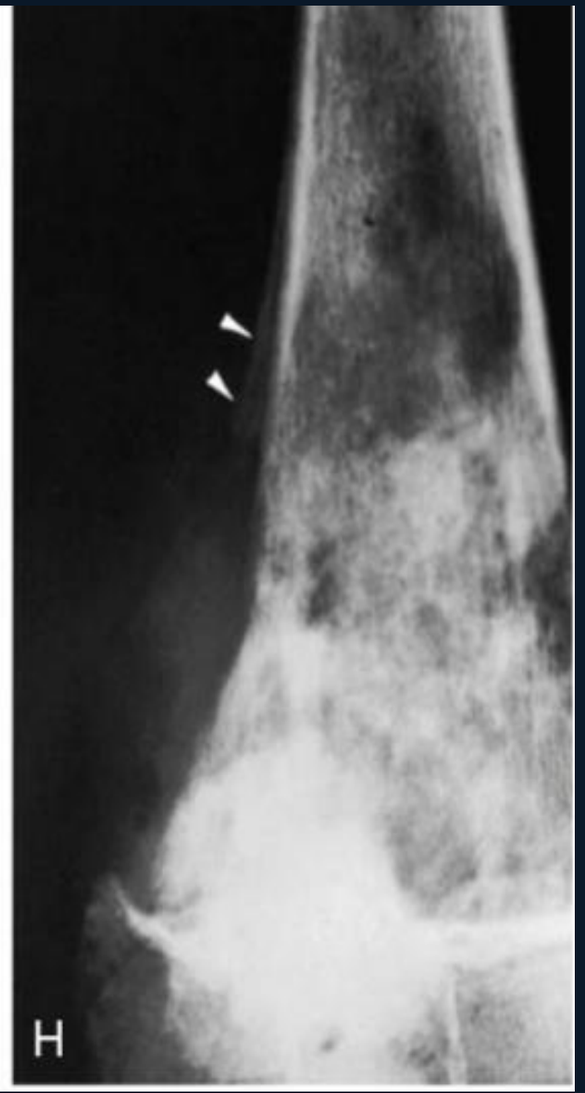
- (Final diagnosis : osteosarcoma)



- **Codman's triangle** (arrowheads)

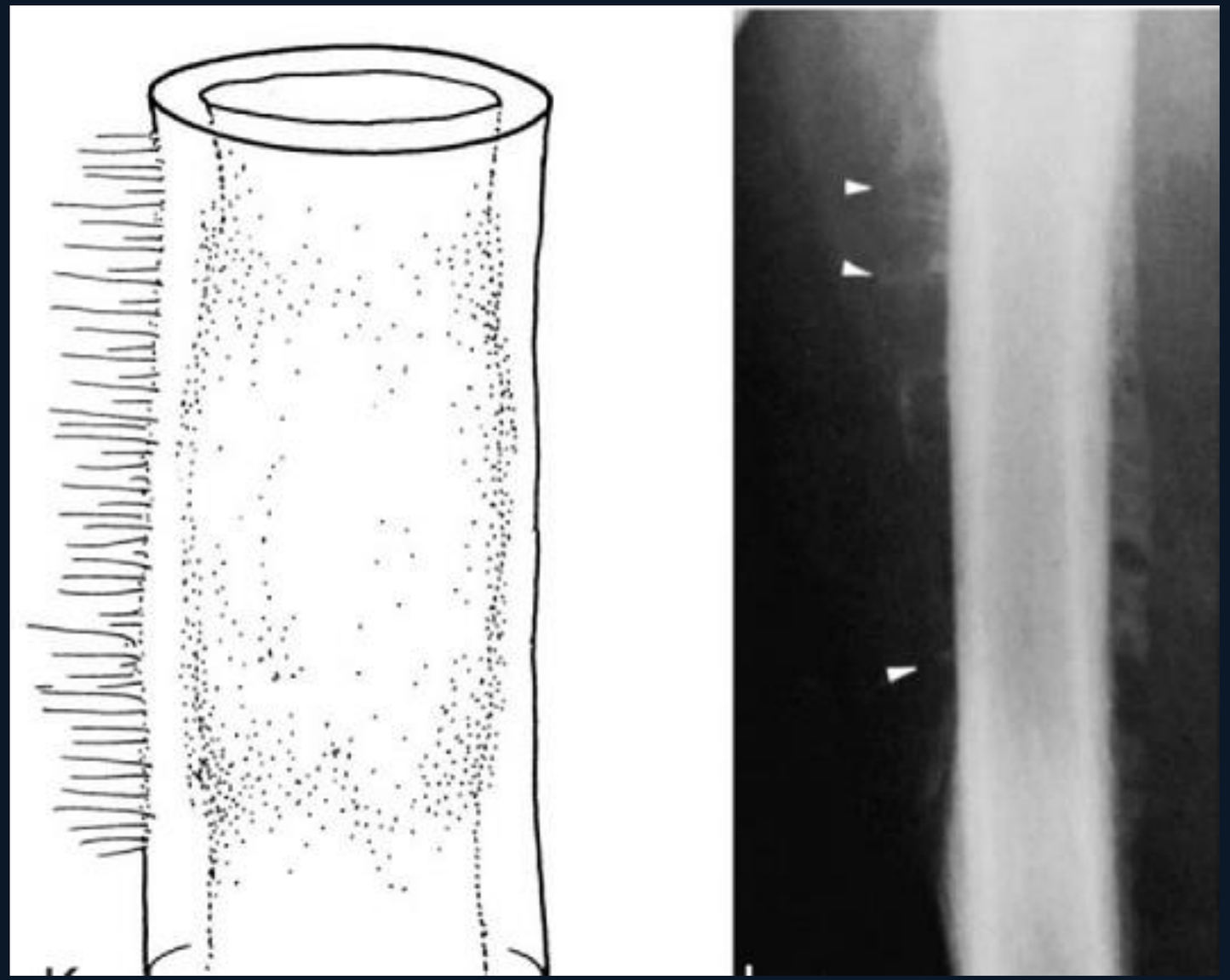
- medullary and cortical bone destruction
- soft tissue mass,
- radiodense foci within the lesion
- (Final diagnosis, osteosarcoma)





➢ hair-on-end pattern

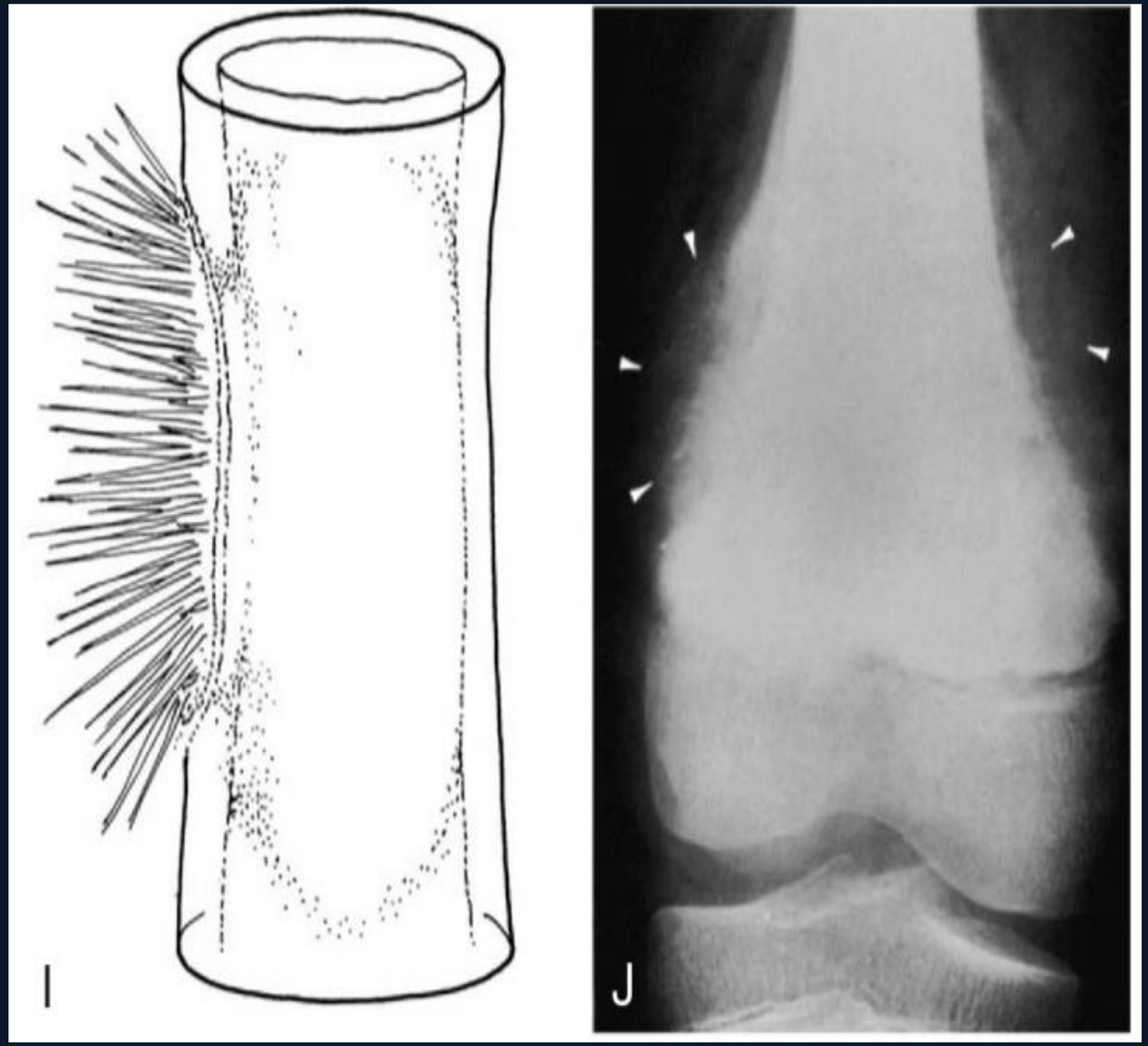
- Final diagnosis :
  Ewing’s sarcoma

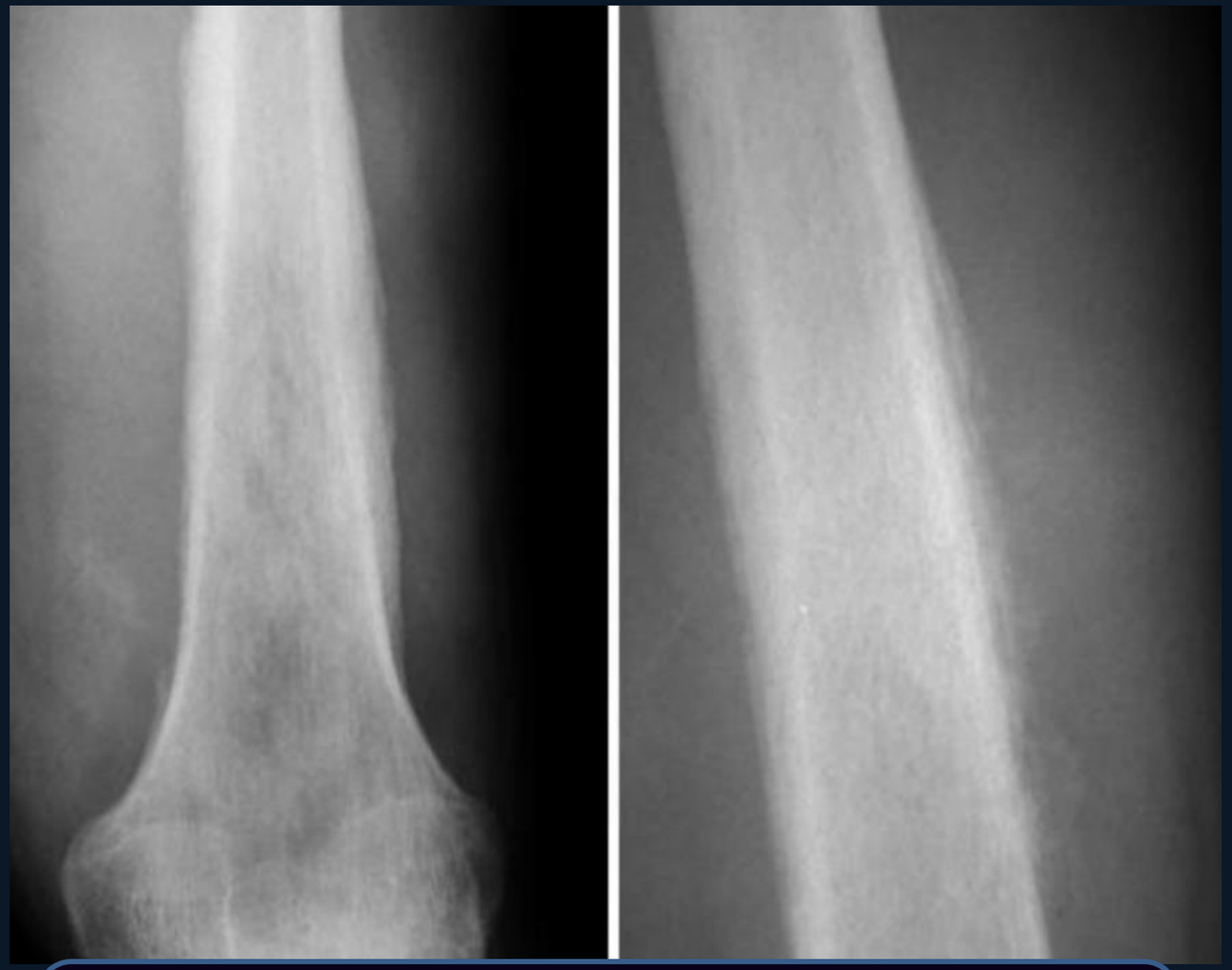


➢ sunburst pattern

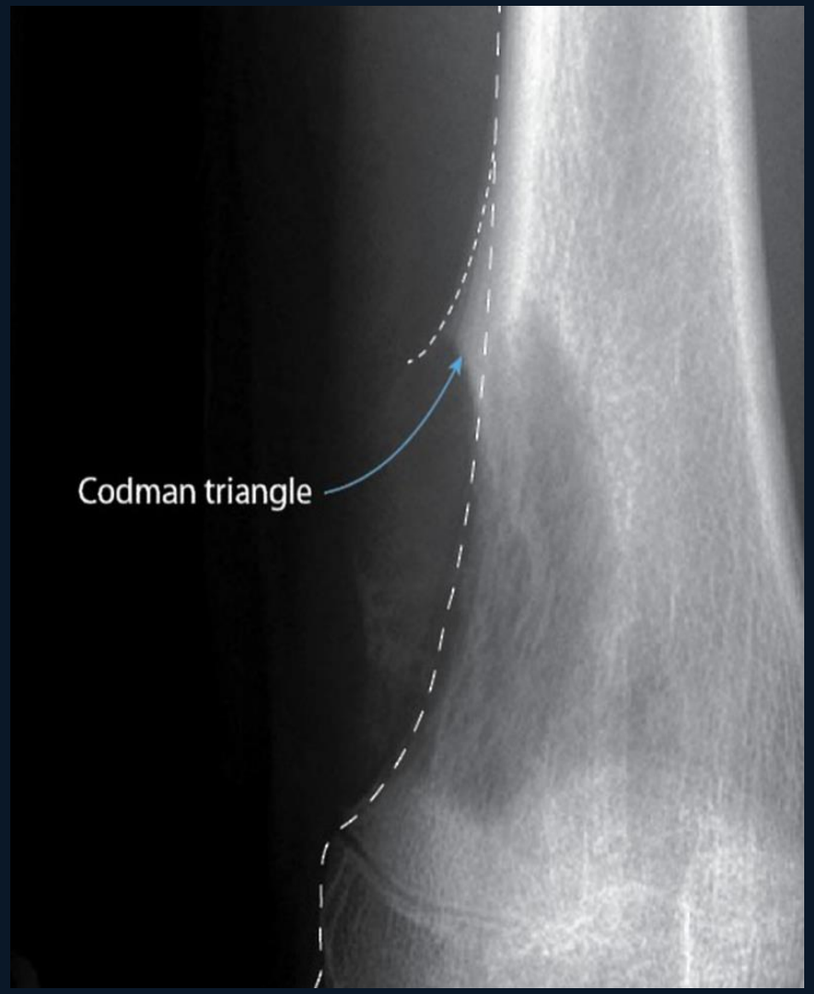
- The radiograph indicates a sunburst pattern of periosteal bone (arrowheads) that is intermixed with tumor bone formation.

(Final diagnosis : osteosarcoma)





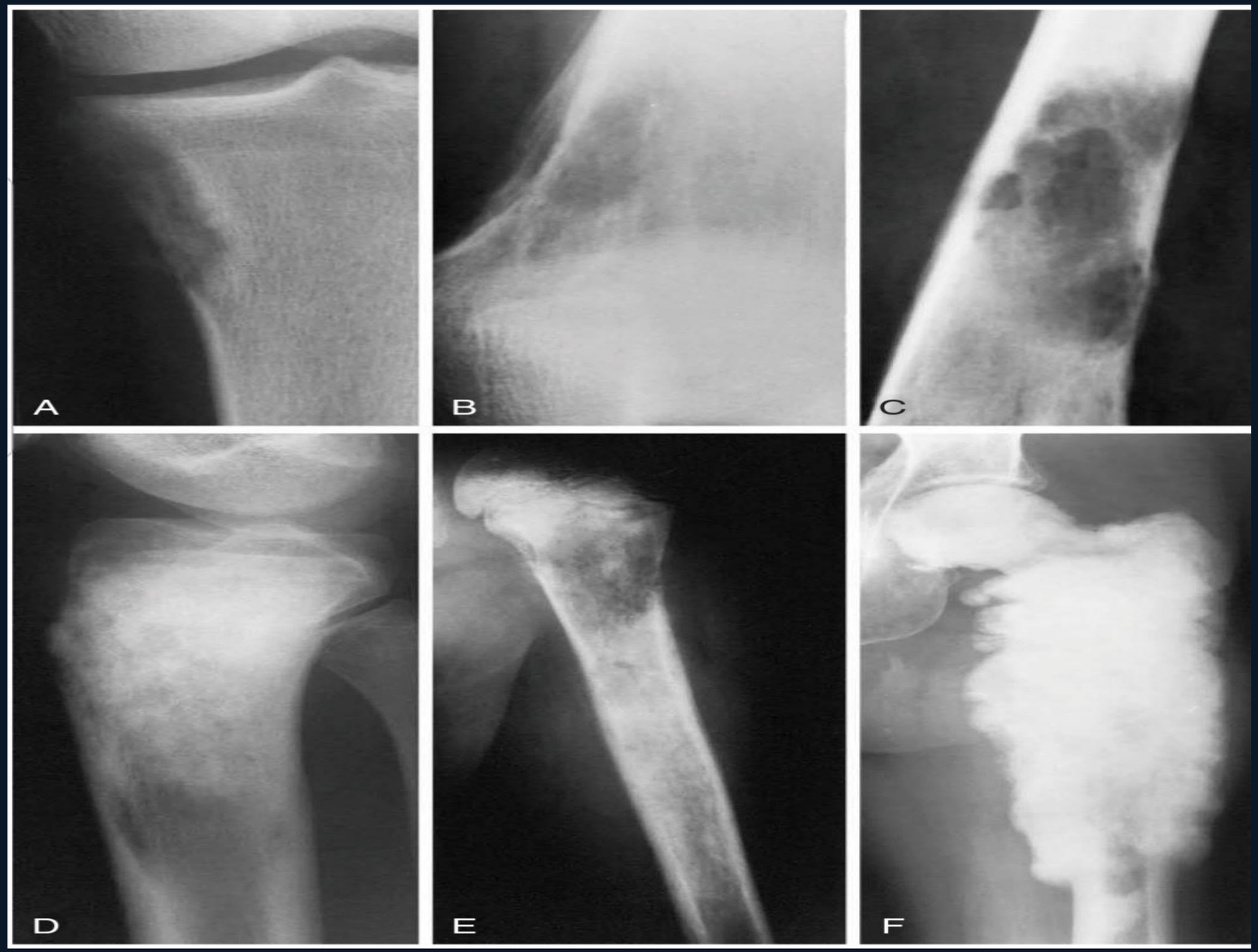
Onion skin periosteal reaction in ewing sarcoma(AP-lat)



osteosarcoma

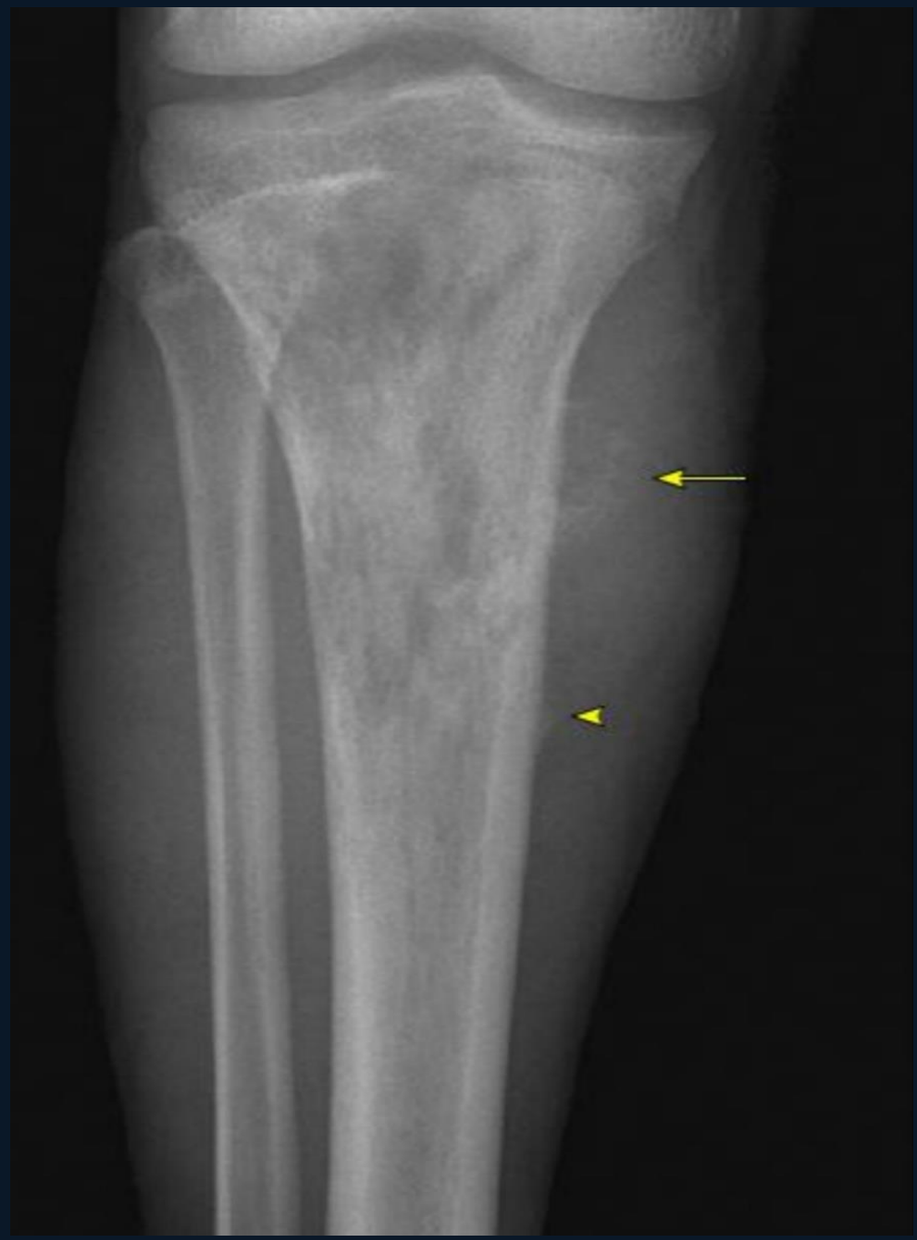
osteosarcoma:

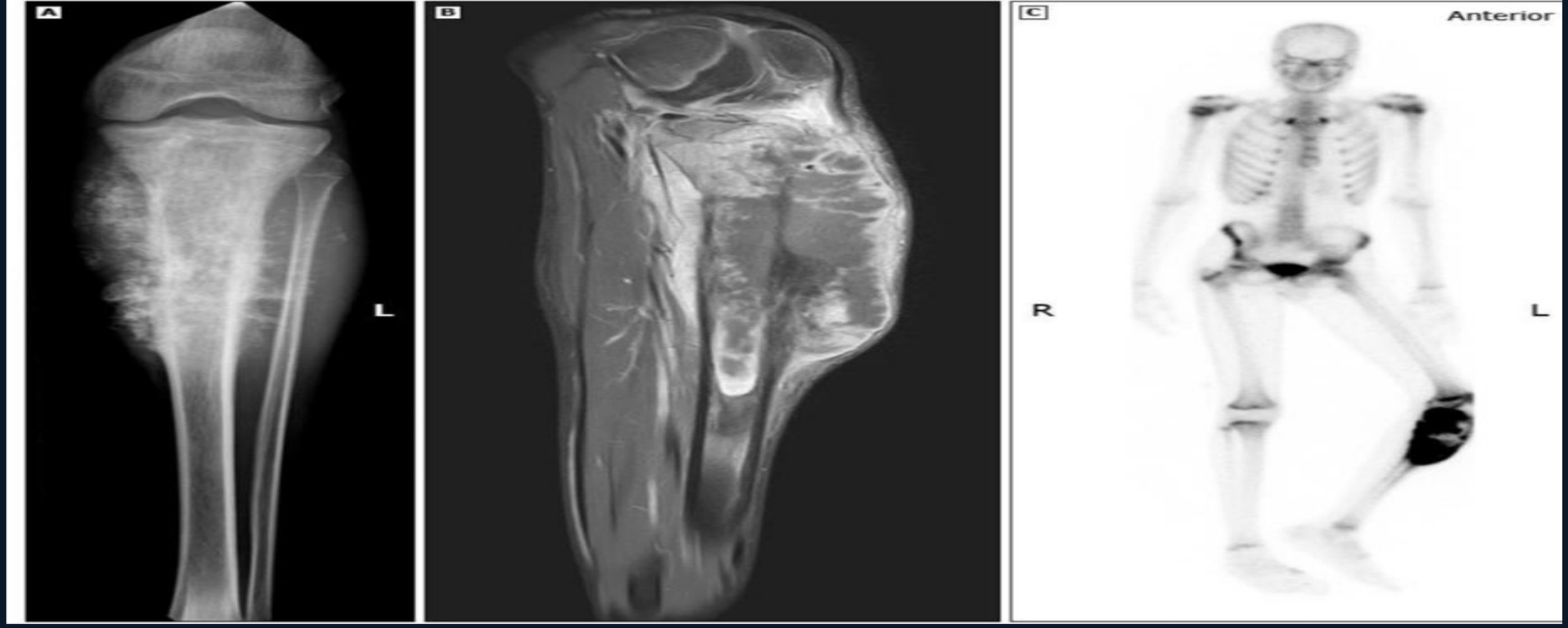
basic patterns of osseous involvement.



➢ Osteosarcoma :

- ✓ Mixed lytic and sclerotic lesion
- ✓ soft tissue involvement
- ✓ codman triangle





osteosarcoma :

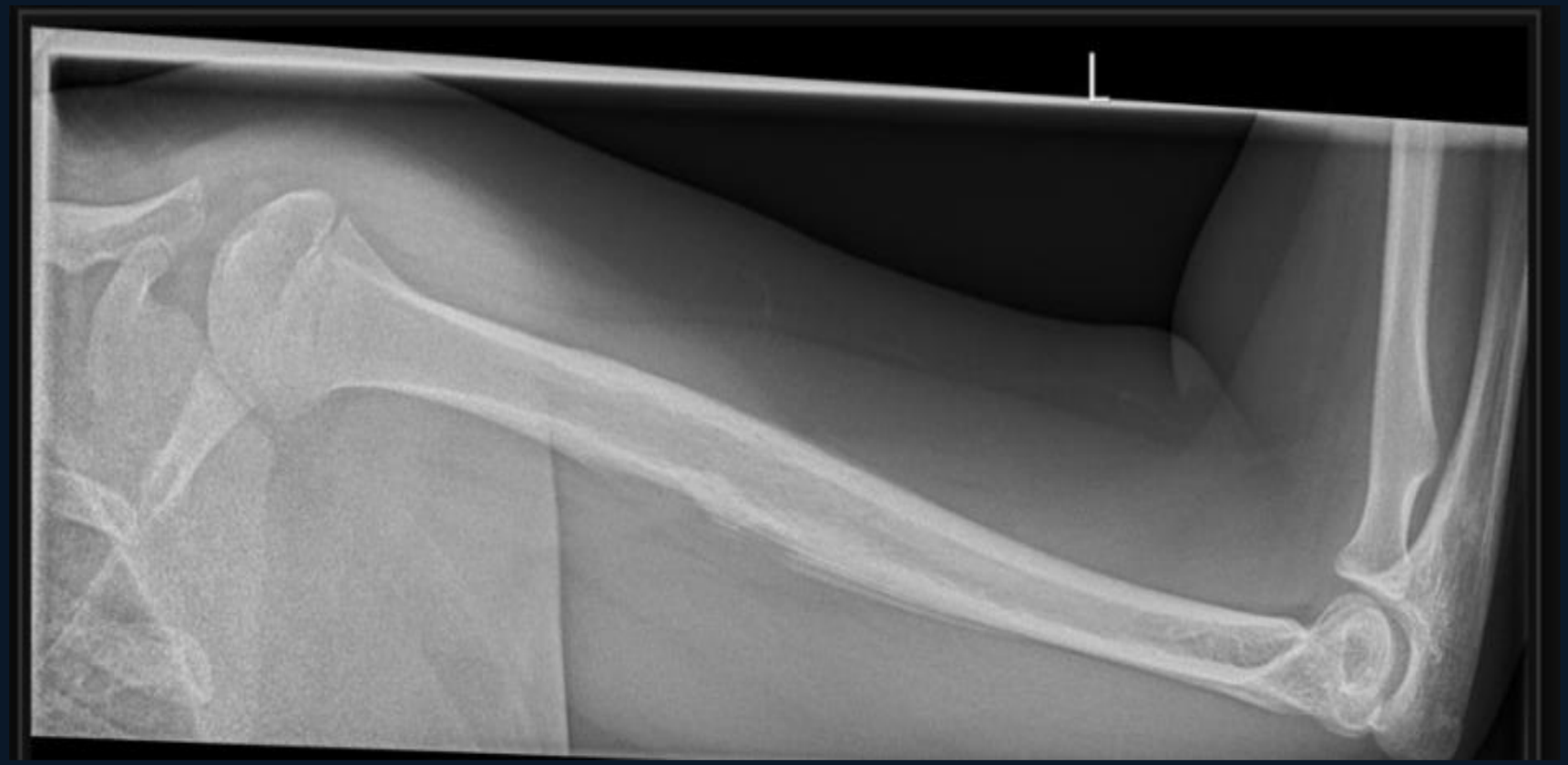
(A) Radiograph of tumor in proximal tibia showing aggressive periosteal reaction with **sunburst appearance.**

(B) T1 + C MRI demonstrating a large **soft tissue mass** associated with the **primary tumor**.

(C) Total body bone scan showing increased radiotracer uptake confined to the primary tibial mass

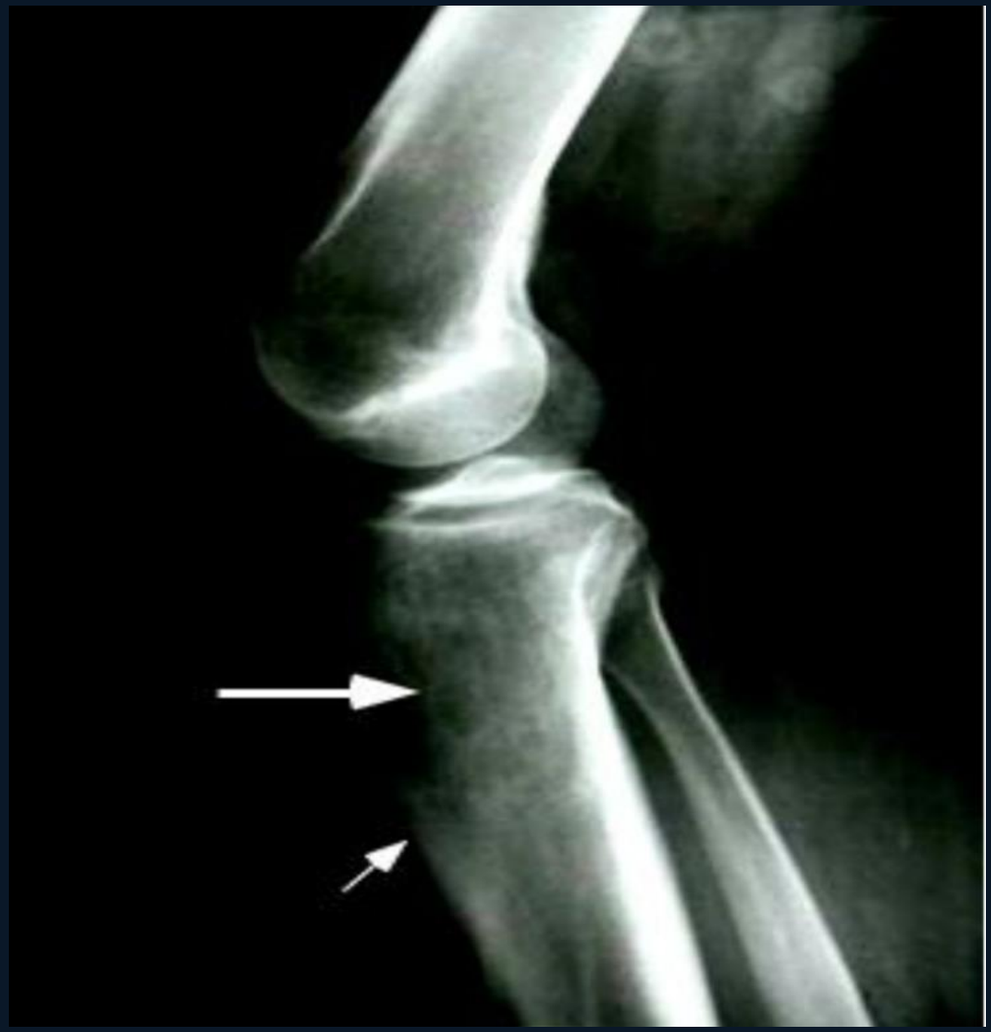
➢ Ewing sarcoma

- ✓ Left hemoral lesion with **permeative appearance**
- ✓ **lamellated periosteal reaction**



Lymphoma of bone

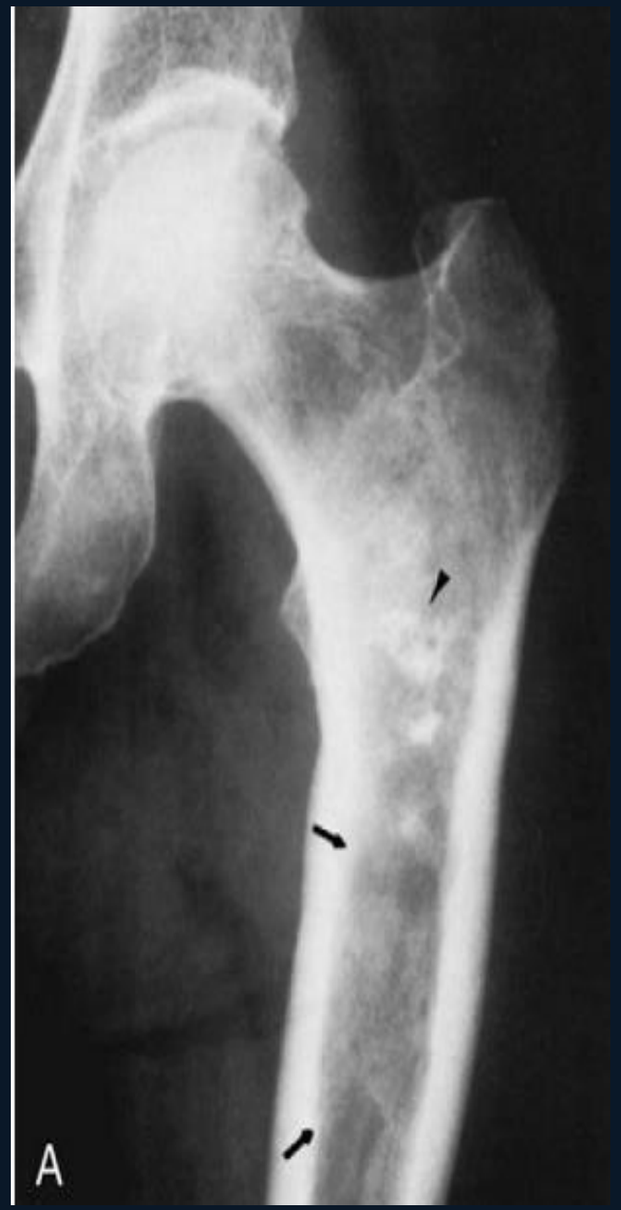
a **"moth-eaten"** pattern in the proximal tibia, along with bone destruction (large arrow).
An associated **periosteal reaction** is present (small arrow)

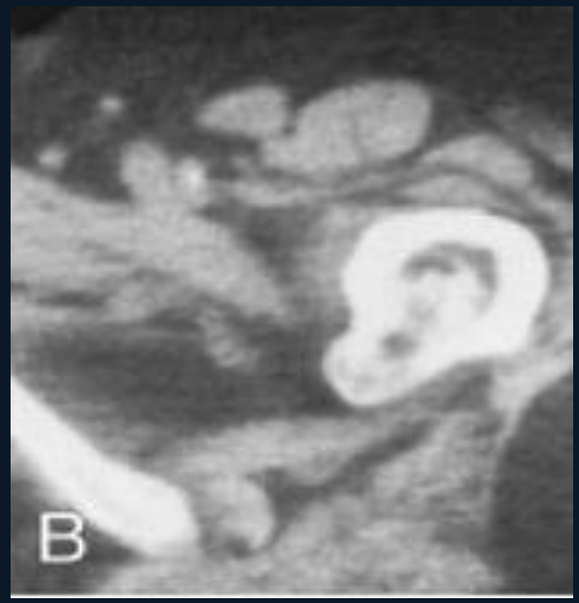


➢ chondrosarcoma

- a routine radiograph (A) shows an expansile lesion of the femoral diaphysis . The proximal portion of the lesion is calcified; the distal portion is not.

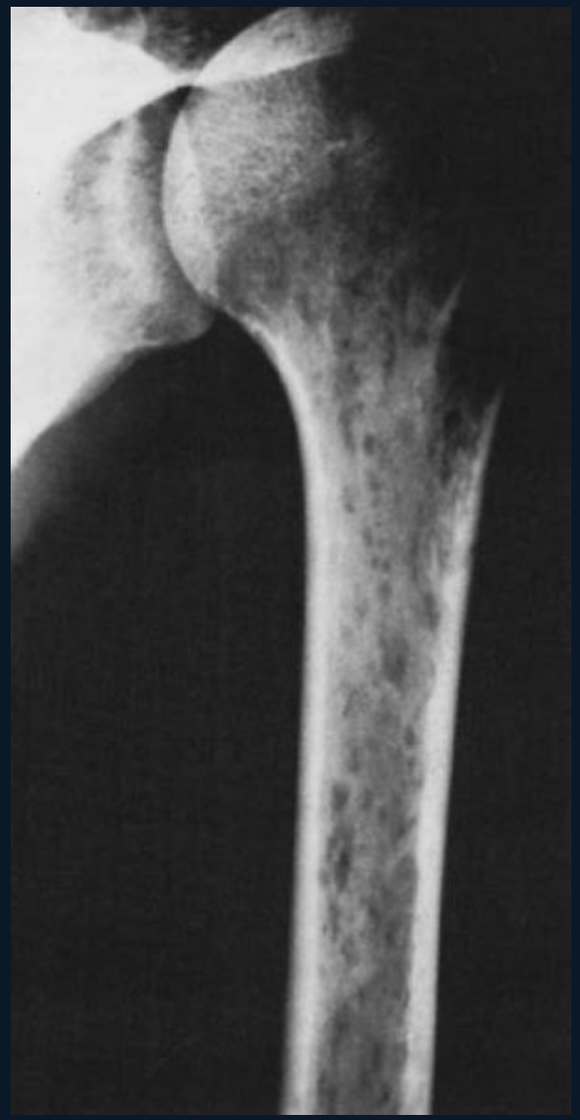
- Transaxial CT scan (B) reveals internal calcifications and cortical erosion



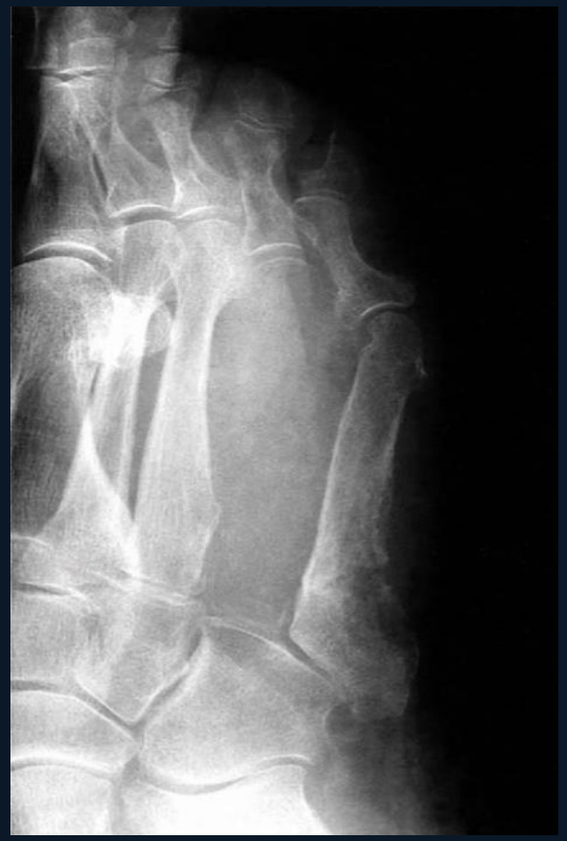


- **Chronic leukemia** : osteolytic lesions.

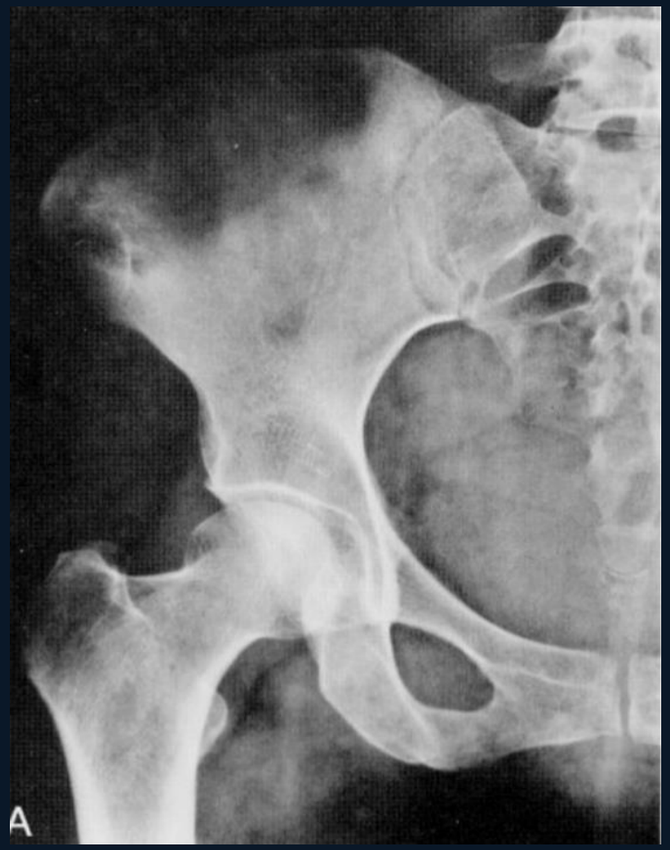
- A 27-yearold woman with chronic leukemia demonstrates small, focal radiolucent lesions



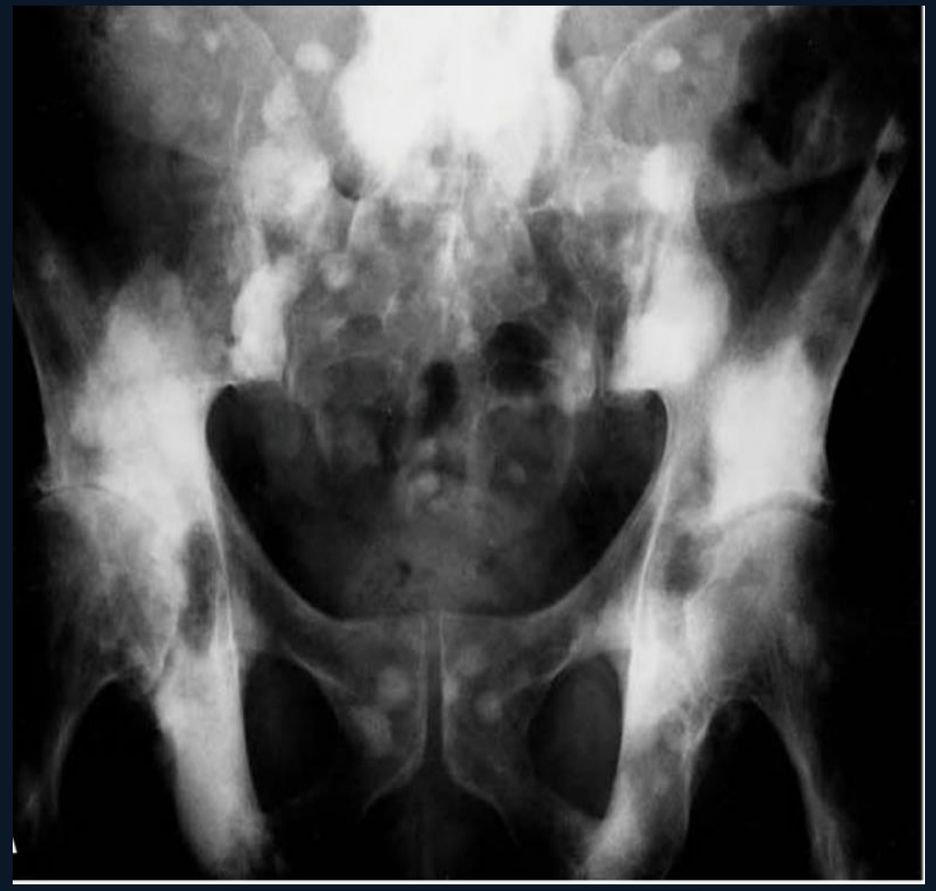
metastasis



purely osteolytic pattern



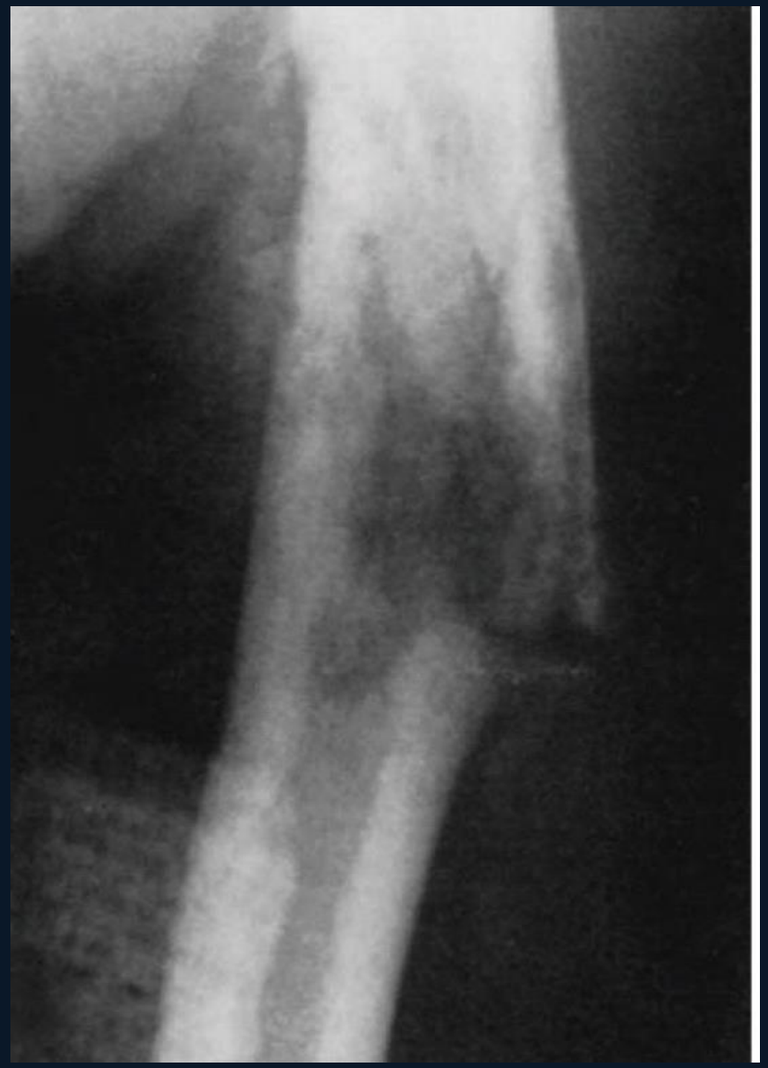
osteolytic-sclrotic pattern



purely sclerotic pattern

➢ Metastasis

- **oblique fracture** has occurred through a **“moth-eaten”** region of bone destruction in the diaphysis of the humerus.



POST-CHEMOTHERAPY RHEUMATIC DISEASE

- Postchemotherapy rheumatism has been best described in patients treated for **breast cancer**, but it also has been described in other malignancies, including **ovarian cancer and NHL**.

- The phenomenon has been described as a **noninflammatory, selflimited, migratory arthropathy** . Typically symptoms develop several weeks to several months after the completion of chemotherapy and often include myalgia, stiffness, arthralgia, and arthritis involving the small joints of the hands, ankles, and knees.

- Post chemotherapy rheumatism can be mistaken for **RA** based on its symptoms;

POST-CHEMOTHERAPY RHEUMATIC DISEASE

- The **pathogenesis** of this process is unknown; however, it is selflimited, usually lasting less than 1 year, and is best treated in a conservative fashion.

- **Evaluation** should be performed to exclude recurrent carcinoma or another inflammatory condition

- The medications most frequently implicated in this phenomenon are cyclophosphamide, 5florouracil, methotrexate, and tamoxifen.

- **Tamoxifen** : an acute inflammatory arthritis similar to RA

- **aromatase inhibitors** : arthralgia and arthritis

POST-CHEMOTHERAPY RHEUMATIC DISEASE

- **Biologic agents** can lead to an autoimmune phenomenon.
- **Use of IL2 :** spondyloarthritis or inflammatory arthritis.
- **Interferon α :** seropositive nodular RA and myalgia and arthralgia.
- The use of **interferon** also can result in **autoantibody formation** and features suggestive of **SLE** and **autoimmune thyroid disease.**

Graft-Versus-Host Disease

- Numerous musculoskeletal symptoms arise in the setting of acute and in chronic GVHD.
- The most frequent manifestation is the involvement of the **skin** , which in many cases can progress to resemble the changes of SSc . Skin changes consistent with **eosinophilic fasciitis** also have been reported.
- GVHD can lead to symptoms of **keratoconjunctivitis sicca and xerostomia.**
- Other features including arthralgias, arthritis, myositis, Raynaud's phenomenon, and serositis also have been reported

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انسان را به شوق و آرامش برساند

روز پزشک مبارک