Аутоиммунные заболевания

Саркоидоз

Саркоидоз

Межсистемное заболевание неизвестной этиологии, которое проявляется образованием неказеозных эпителиоидных гранулем в пораженных органах.

Могут быть поражены любые органы, но чаще это легкие и внутригрудные лимфоузлы.

Для саркоидоза нет ничего патогномоничного, также как и не существует высокоспецифичных тестов.

Отсутствуют способы прогнозировать дальнейшее развитие заболевания.

Отсутствует специфическая терапия.

Эпидемиология

- Распространен повсеместно; в Европе и США 10-64 случаев на 100 000 ежегодно. Чаще болеют афроамериканцы и северные народы.
- Могут заболеть люди любого возраста, но 80% случаев приходятся на промежуток 20-50 лет.
- Среди различных популяций варьируют клинические проявления.
- Летальные исходы <1-6%. Основные причины: легочные, сердечно-сосудистые, неврологические.

Этиология

- ACCESS (A Case Controlled Etiologic Study of Sarcoidosis)
- 704 обследованных
- Небольшая вероятность наследственной предрасположенности 5-16%. Обычно генетическая предрасположенность коррелирует с генами MHC II класса. Однако имеются существенные этнические различия.
- Нет определенных данных о воздействии окружающей среды. Предполагается, что чаще болеют работники здравоохранения, военные и пожарные.
- Имеются данные об участии M. Tuberculosis, Proprionibacterium acne, P. Granulosum в качестве одних из триггерных факторов.
- Заболевание чаще проявляется в весенние месяцы

Патогенез

- Теория мисфолдинга САА
- Индуктором является инфекционный агент (m.tuberculosis, p. acne) - mKatG
- Гиперактивация Th1-иммунного ответа
- Сывороточный амилоид А является провоспалительным веществом для скопления иммунных клеток и образования гранулем
- От качества «очистки» антигенов и САА зависит исход

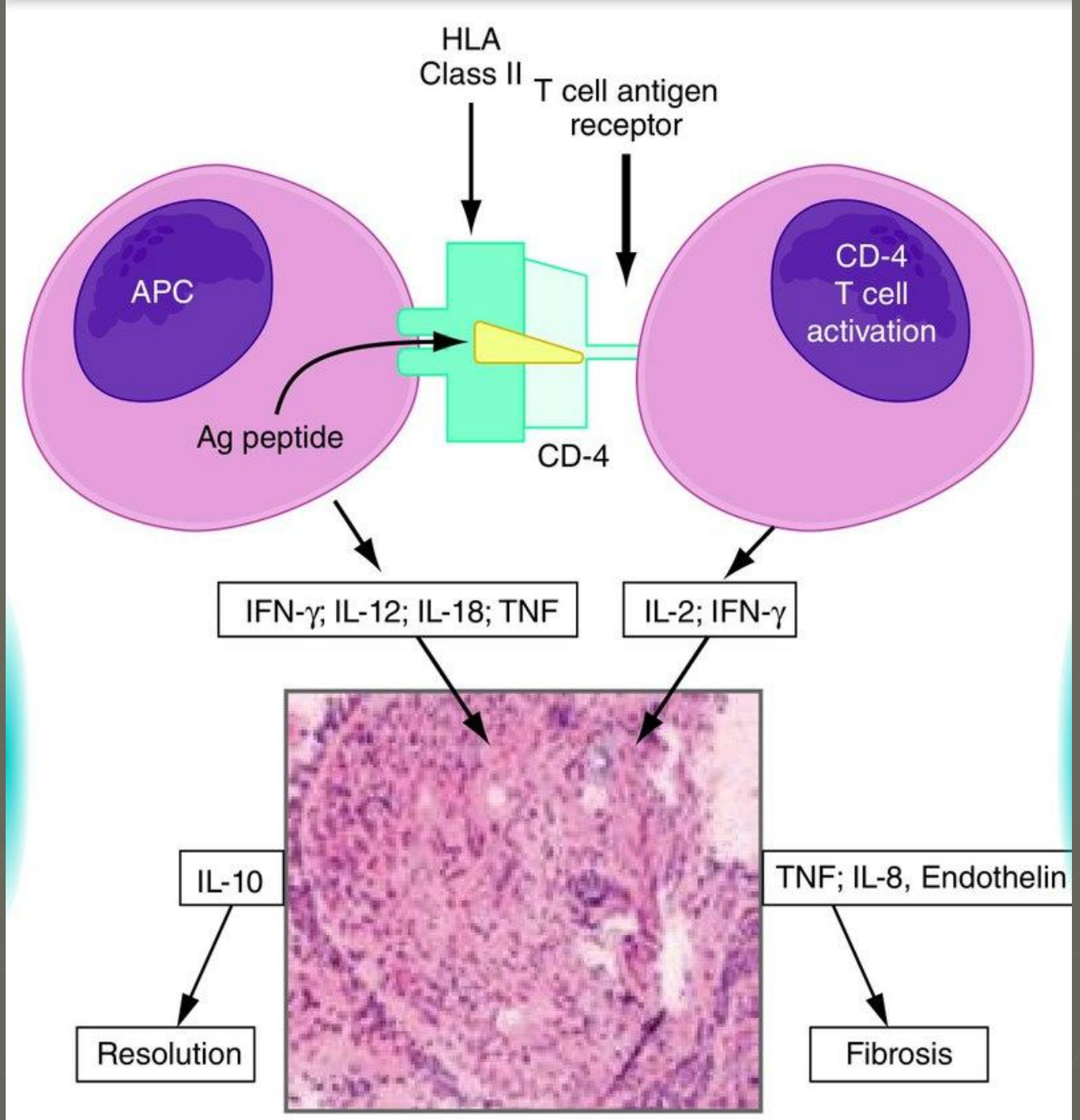


FIGURE 390-1 Schematic representation of initial events of

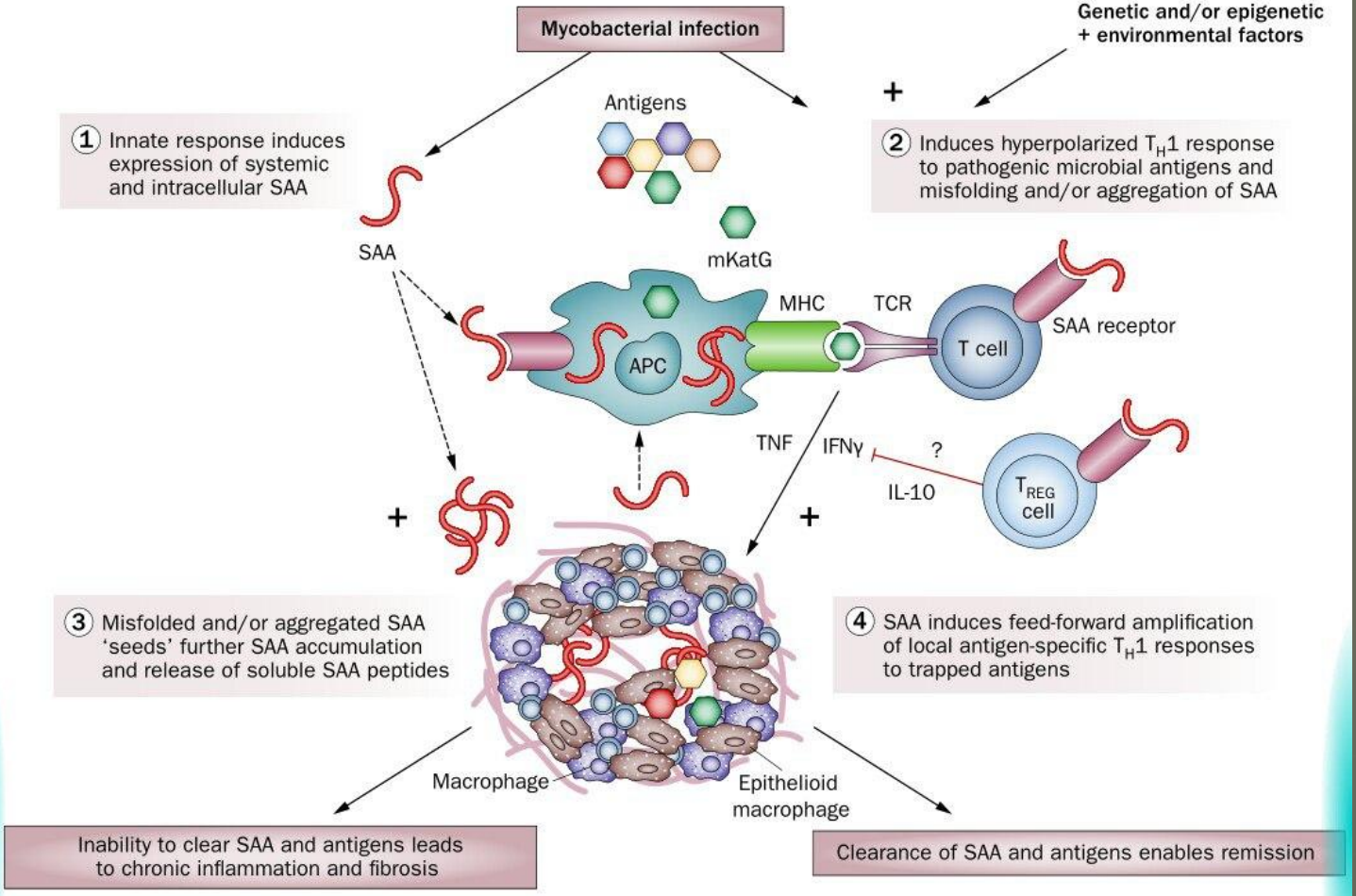
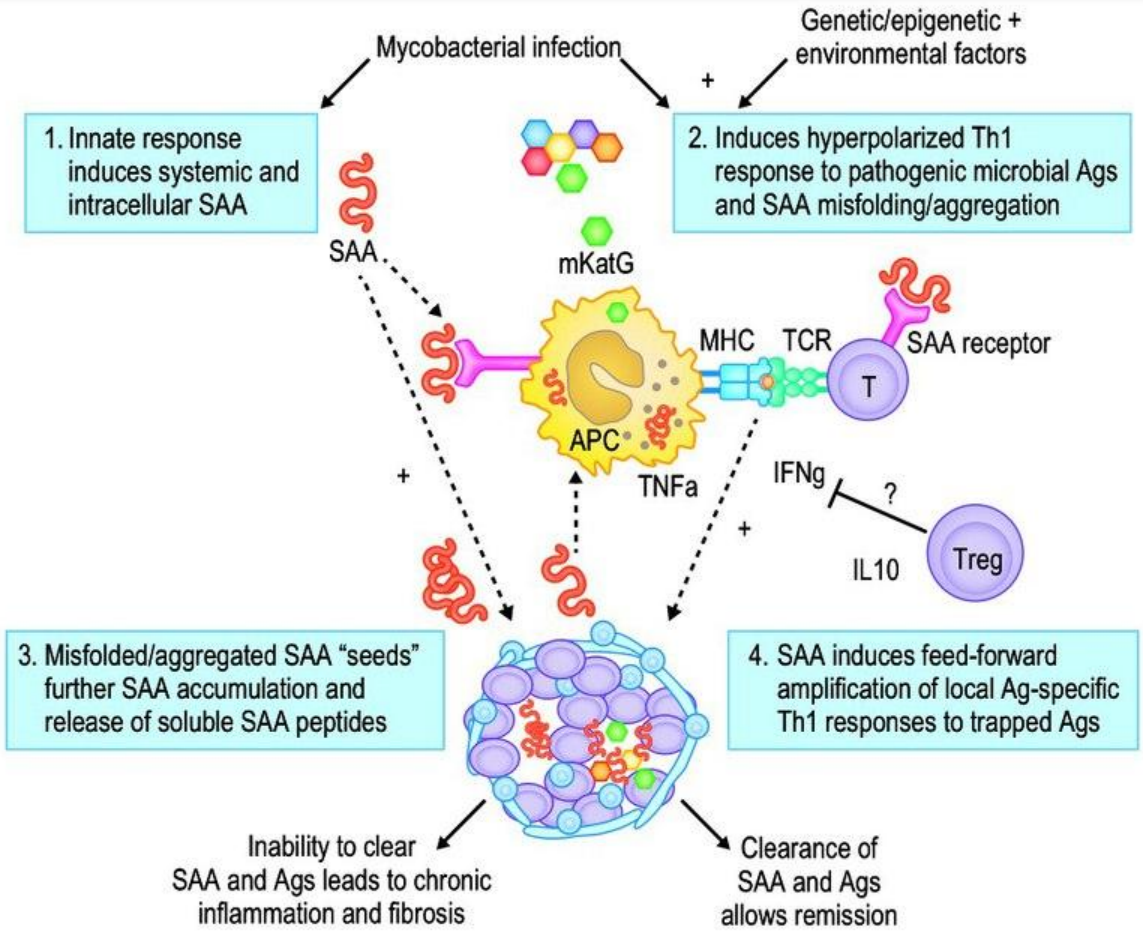


Figure 1 | Serum amyloid A misfolding hypothesis of the pathobiology of sarcoidosis. In this scenario, misfolded SAA aggregates serve as 'seeds', providing a poorly soluble nidus and a template for further SAA aggregation within sarcoidosis granulomas by an amyloid-like process.[37] SAA and SAA peptides released from the granulomas cause the feed-forward stimulation of macrophages and T cells, in part through TLR2. This stimulation results in the amplification of polarized T_H1 responses to local pathogenic antigens with production of TNF, T_H1-promoting cytokines and IL-10 (which partially dampens the inflammatory response). Tissue antigens might derive from degradation-resistant microbial antigens, new microbial antigens trapped by the granuloma or from induction of autoimmune responses. This pathobiologic course continues unabated unless there is clearance of aggregated SAA and local pathogenic antigens together with downregulation of T_H1 responses. Although the model depicts mycobacterial organisms as inciting agents, nonmycobacterial microbes or environmental agents could trigger a similar pathobiologic outcome. Abbreviations: APC, antigen-presenting cell; IFN, interferon; SAA, serum amyloid A; TCR, T cell receptor; T_H1, type 1 T helper cell; TLR, Toll-like receptor, TNF, tumor necrosis factor. Reprinted with permission of the American Thoracic Society. © American Thoracic Society. Adapted from Chen, E. S. *et al*. Serum Amyloid A regulates granulomatous inflammation in sarcoidosis through Toll-like receptor 2. *Am. J. Resp. Crit. Care Med*. **181**, 360–373 (2010).

Fig. 72.2 Conceptual model of the immunopathogenesis of sarcoidosis. Granuloma formation in sarcoidosis results from stimulation by poorly soluble antigens that evoke a hyperimmune Th1 response with stimulation of INF-γ, along with TNF, IL-12, IL-10, and other cytokines from mononuclear phagocytes and dendritic cells. As a consequence of this response, misfolded SAA aggregates in an amyloid-like process to provide a persistent poorly soluble nidus and a template for further SAA aggregation within sarcoidosis granulomas. SAA and SAA peptides released from the granulomas stoke a feed-forward stimulation of macrophages and T cells that amplifies polarized Th1 responses to local tissue antigens. This course continues to progress unless there is removal of stimulating antigen(s) and clearance of SAA, allowing remission of Th1-driven granuloma formation. The model depicts mycobacterial organisms as the etiologic trigger, though other microbes or environmenal agents might trigger a similar pathogenic pathway.



Диагностика

TABLE 390-1 FREQUENCY OF COMMON ORGAN INVOLVEMENT AND LIFETIME RISK[a]

	Presentation, %[b]	Follow-Up, %[c]
Lung	95	94
Skin	24	43
Eye	12	29
Extrathoracic lymph node	15	16
Liver	12	14
Spleen	7	8
Neurologic	5	16
Cardiac	2	3

Table 72.1 Major clinical features of systemic sarcoidosis

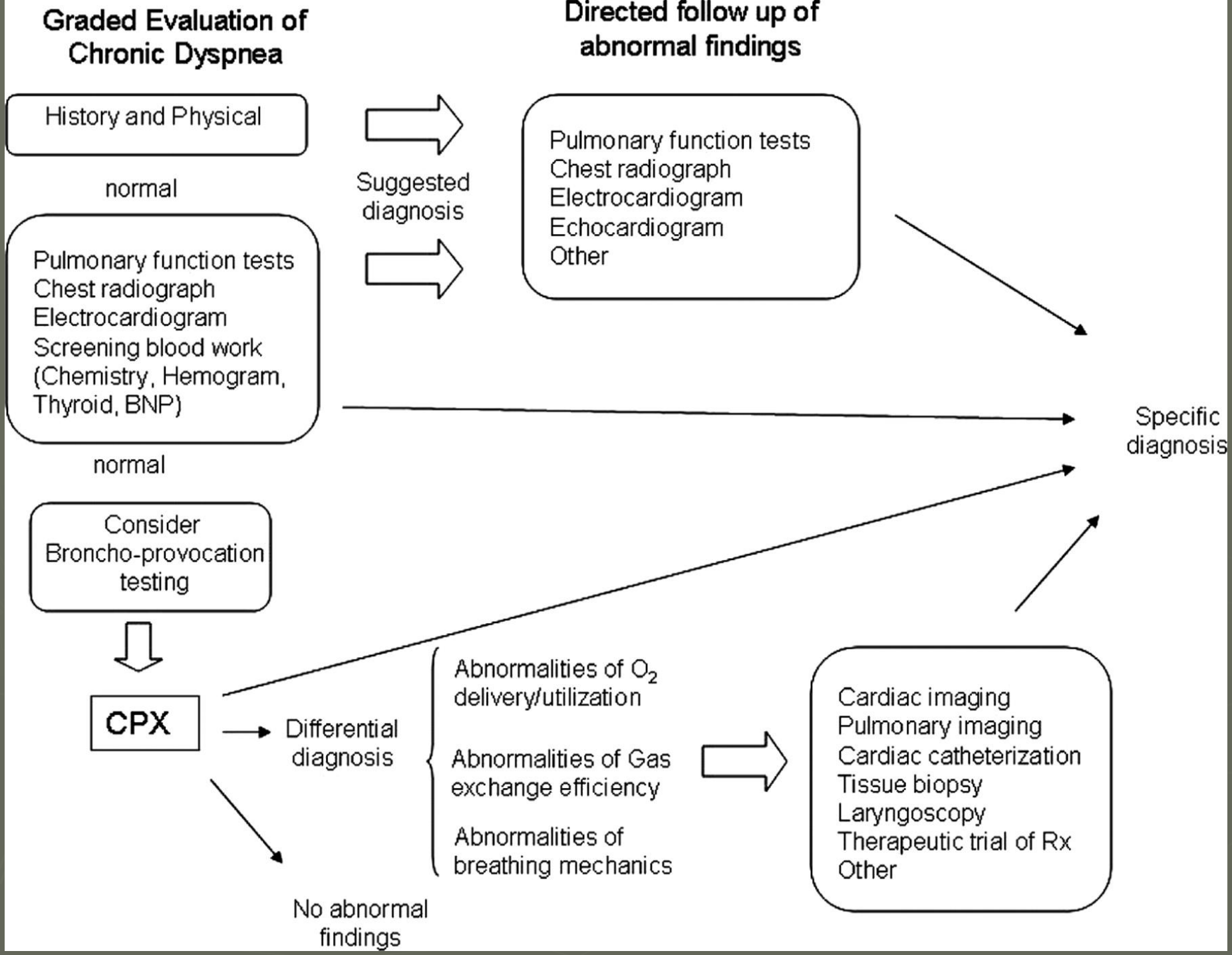
Organ system (approx. % involvement)	Major clinical features
Pulmonary (90)	Bilateral hilar adenopathy, restrictive and obstructive disease, fibrocystic disease, bronchiectasis, mycetomas
Upper airway (5–10)	Hoarseness, laryngeal or tracheal obstruction, nasal congestion, sinusitis, saddle nose deformity
Ocular (25)	Anterior and posterior uveitis, chorioretinitis, conjunctivitis, optic neuritis, glaucoma, lacrimal gland enlargement
Skin (20)	Erythema nodosum, chronic nodules and plaques, lupus pernio, alopecia
Hepatic (10)	Hepatomegaly, pruritus, jaundice, cirrhosis
Cardiac (5–10)	Arrhythmias, heart block, cardiomyopathy, sudden death
Central nervous system (5–10)	Cranial neuropathy, e.g., Bell's palsy, aseptic meningitis, brain mass, seizures, obstructing hydrocephalus, myelopathy, polyneuropathy, mononeuritis multiplex
Salivary and parotid gland (10)	Salivary and parotid gland enlargement, sicca syndrome
Hematologic (30–50)	Lymphadenopathy, splenomegaly, hypersplenism, anemia, lymphopenia, thrombocytopenia
Joints/ musculoskeletal (10–20)	Polyarthritis, bone cysts, Achilles' tendonitis, heel pain, myopathy
Endocrine (<10)	Hypercalciuria (more common), hypercalcemia, hypopituitarism, diabetes insipidus
Renal (<5)	Renal calculi, nephrocalcinosis, renal failure, epididymitis, testicular mass

Table 1 | Common clinical manifestations of sarcoidosis

Affected organ	Frequency of occurrence (%)	Common findings
Lungs and thoracic lymph nodes	>90	Dyspnea, cough, chest pain, pulmonary hypertension, mixed pulmonary function test abnormalities (obstruction, restriction, diffusion deficits)
Skin	20–30	Nodules, plaques, lupus pernio, erythema nodosum (a nongranulomatous panniculitis)
Eyes	20–25	Uveitis, conjunctivitis, lacrimal gland enlargement, sicca syndrome, optic neuropathy
Liver and/or spleen	10–20	Hepatosplenomegaly, jaundice, elevated liver function tests, cirrhosis, hypersplenism
Cardiovascular system	10–20	Ectopy, heart block, arrhythmias, cardiomyopathy, sudden death
Central nervous system	10–25	Cranial neuropathy, mass lesions, aseptic meningitis and/or encephalitis, myelitis, spinal cord and peripheral neuropathy, small fiber neuropathy, pain, hypothalamic–pituitary involvement
Sinuses and upper respiratory tract	5–10	Chronic sinusitis, laryngeal involvement, parotid gland involvement
Bones, joints, muscle	5–15	Chronic arthritis, dactylitis, lytic bone lesions, myopathy
Hematologic system	>50	Peripheral lymphopenia, hypergammaglobulinemia
Renal system (including calcium abnormalities)	5–10	Hypercalcemia and/or hypercalciuria, nephrocalcinosis, nephrolithiasis
Endocrine system	5–10	Hypothalamic–pituitary involvement, pancreatic mass, Heerfordt syndrome (uveoparotid fever)
Gastrointestinal and reproductive tract	<1	Gastric nodules, ovarian or testicular masses

Tests recommended for an initial evaluation of a patient with sarcoidosis

- Chest radiograph
- Pulmonary function tests
  - Spirometry
  - Diffusing capacity
  - Lung volumes
  - Flow–volume loop (if suspected upper airway obstruction)
- Slit-lamp examination (to exclude subclinical uveitis)
- Liver and renal function tests
- Calcium level
- Complete blood count
- Electrocardiogram
- Purified protein derivative skin test


Graded Evaluation of Chronic Dyspnea
Directed follow up of abnormal findings
History and Physical
normal
Pulmonary function tests
Chest radiograph
Electrocardiogram
Screening blood work (Chemistry, Hemogram, Thyroid, BNP)
normal
Consider Broncho-provocation testing
CPX
Suggested diagnosis
Pulmonary function tests
Chest radiograph
Electrocardiogram
Echocardiogram
Other
Specific diagnosis
Differential diagnosis
Abnormalities of O_2 delivery/utilization
Abnormalities of Gas exchange efficiency
Abnormalities of breathing mechanics
No abnormal findings
Cardiac imaging
Pulmonary imaging
Cardiac catheterization
Tissue biopsy
Laryngoscopy
Therapeutic trial of Rx
Other

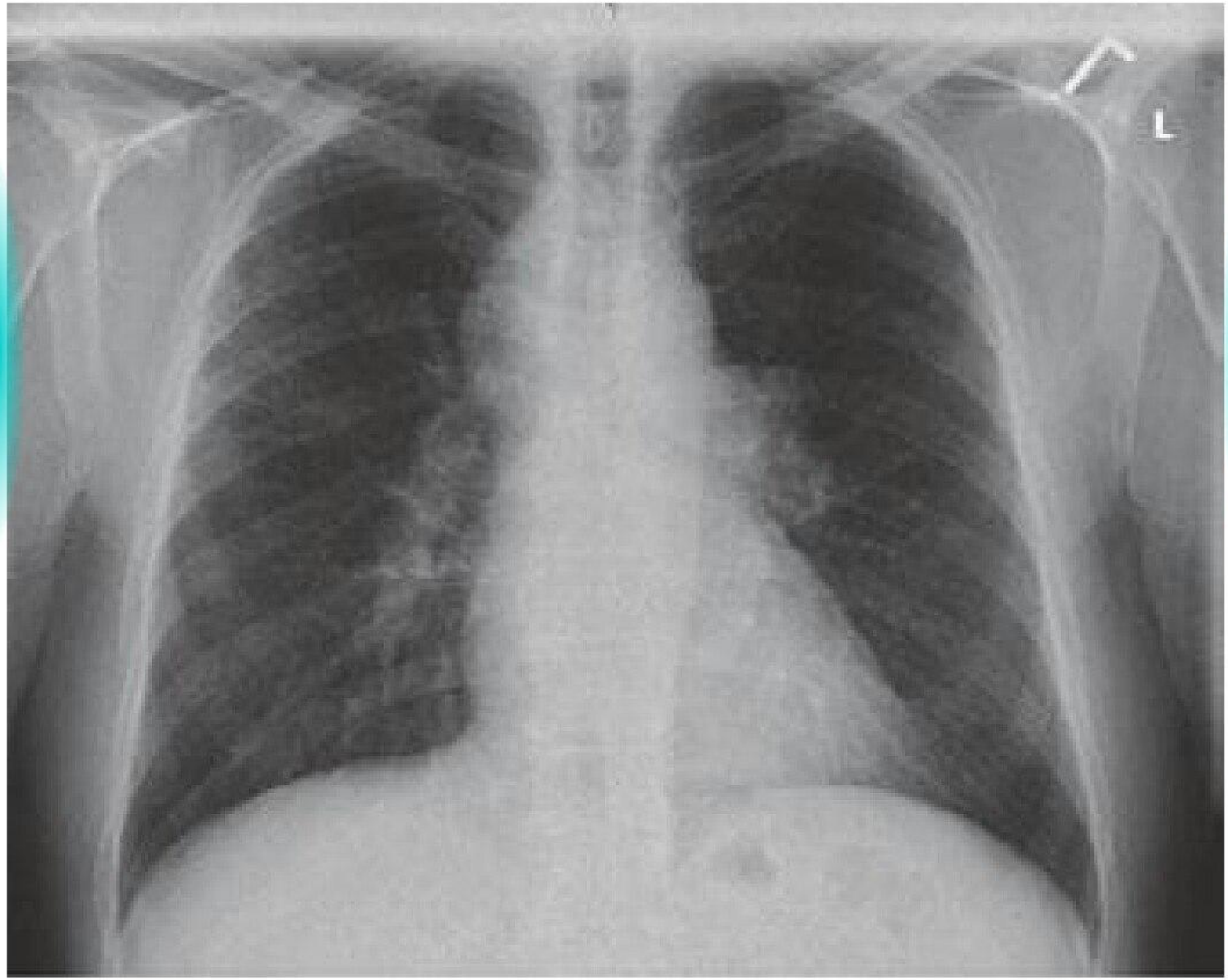


FIGURE 390-2 **Posterior-anterior chest roentgenogram** demonstrating bilateral hilar adenopathy, stage 1 disease.

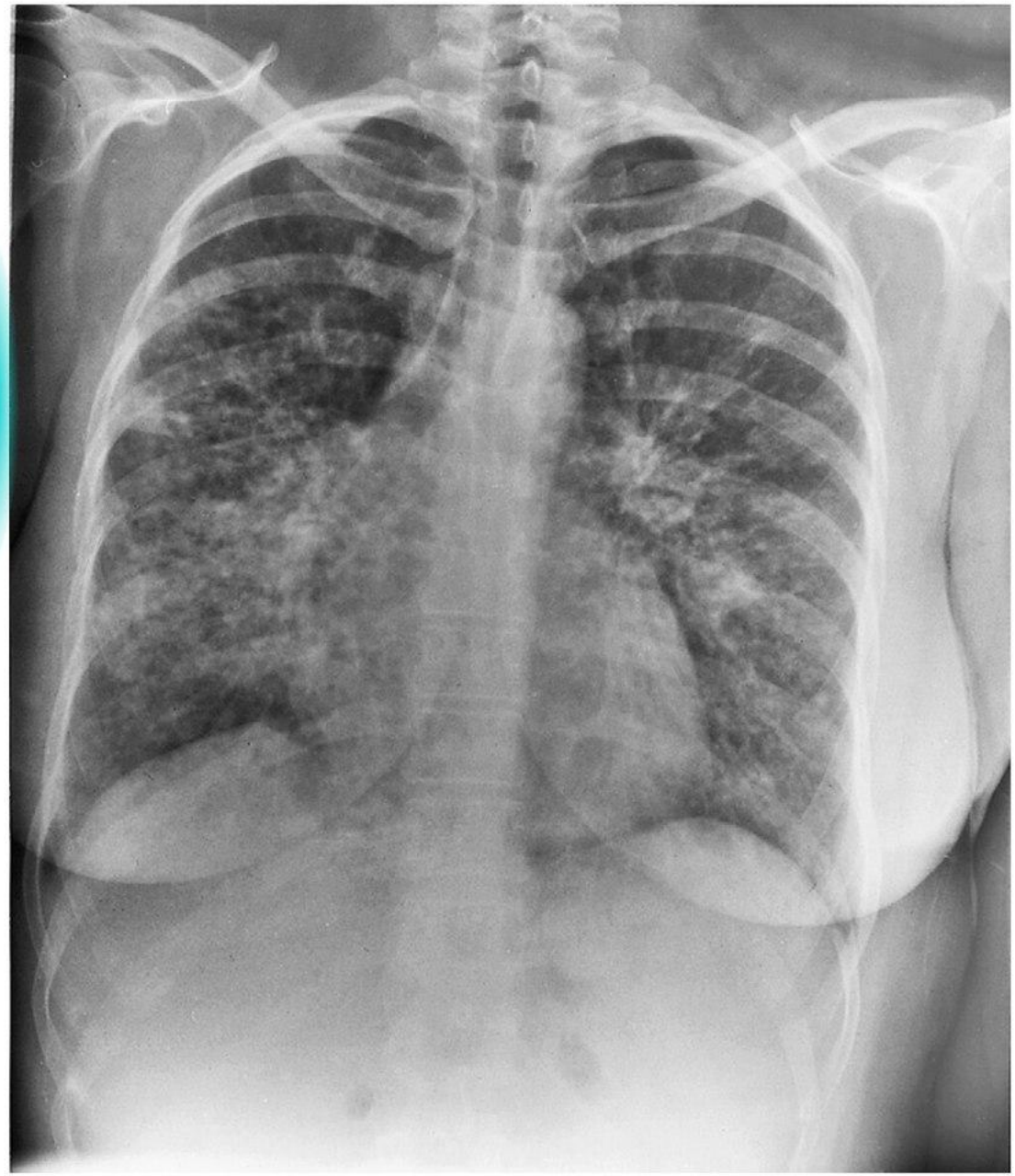


Fig. 72.3 Chest radiograph demonstrating a stage II pattern with bilateral hilar adenopathy and reticulonodular infiltrates.

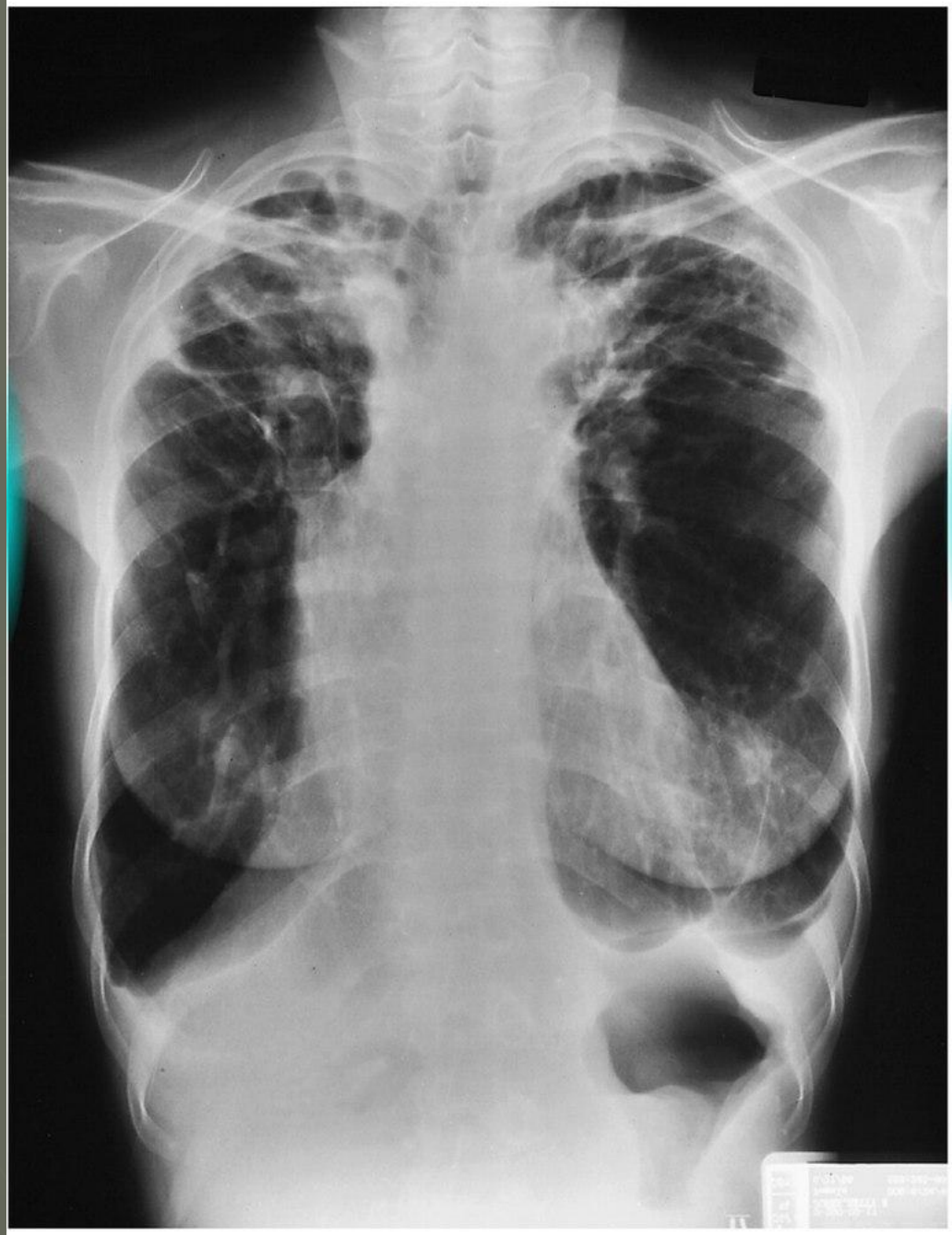


Fig. 72.4 Fibrocystic (stage IV) pulmonary sarcoidosis with typical upward hilar retraction and multiple cystic and bullous changes.

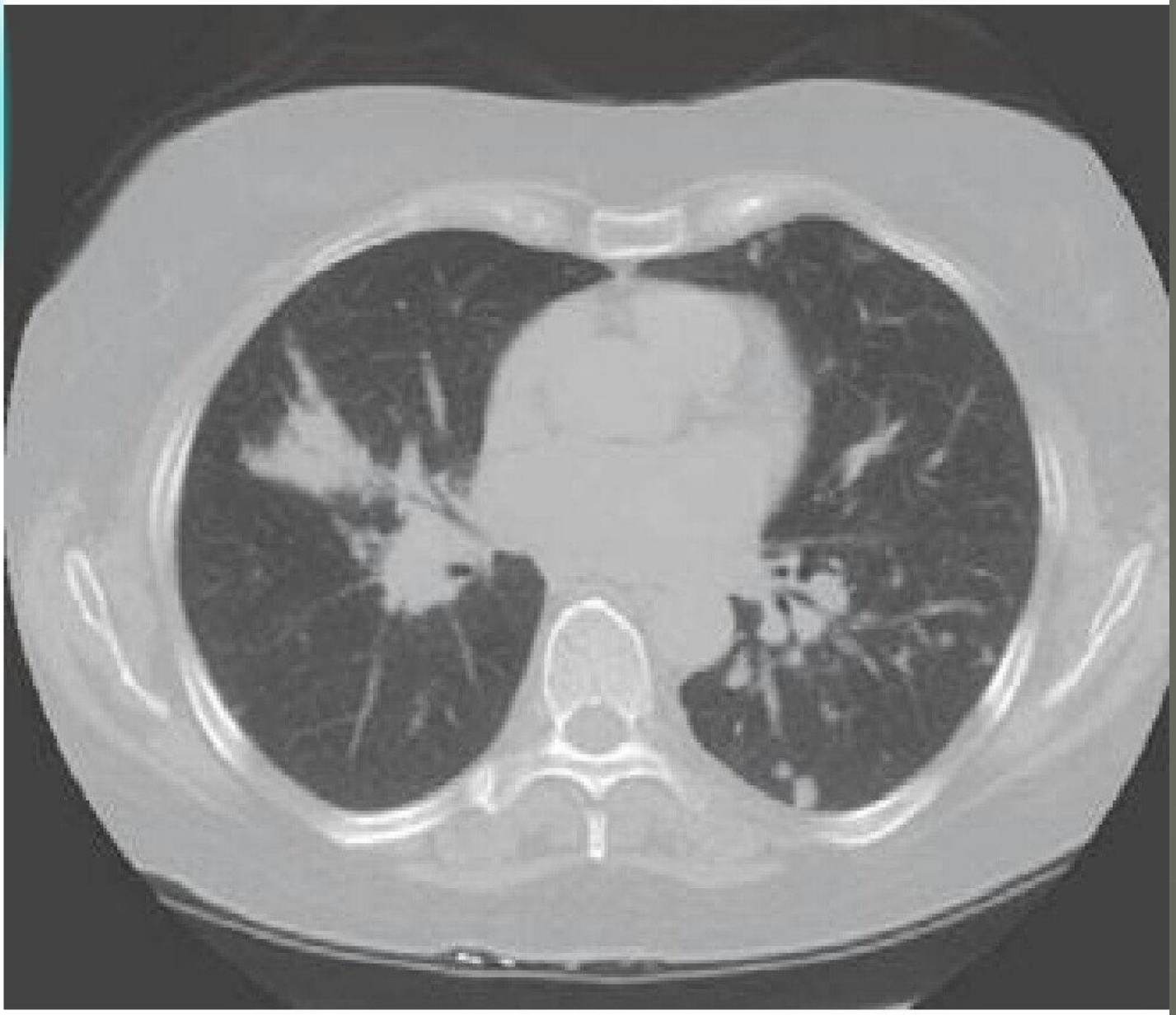
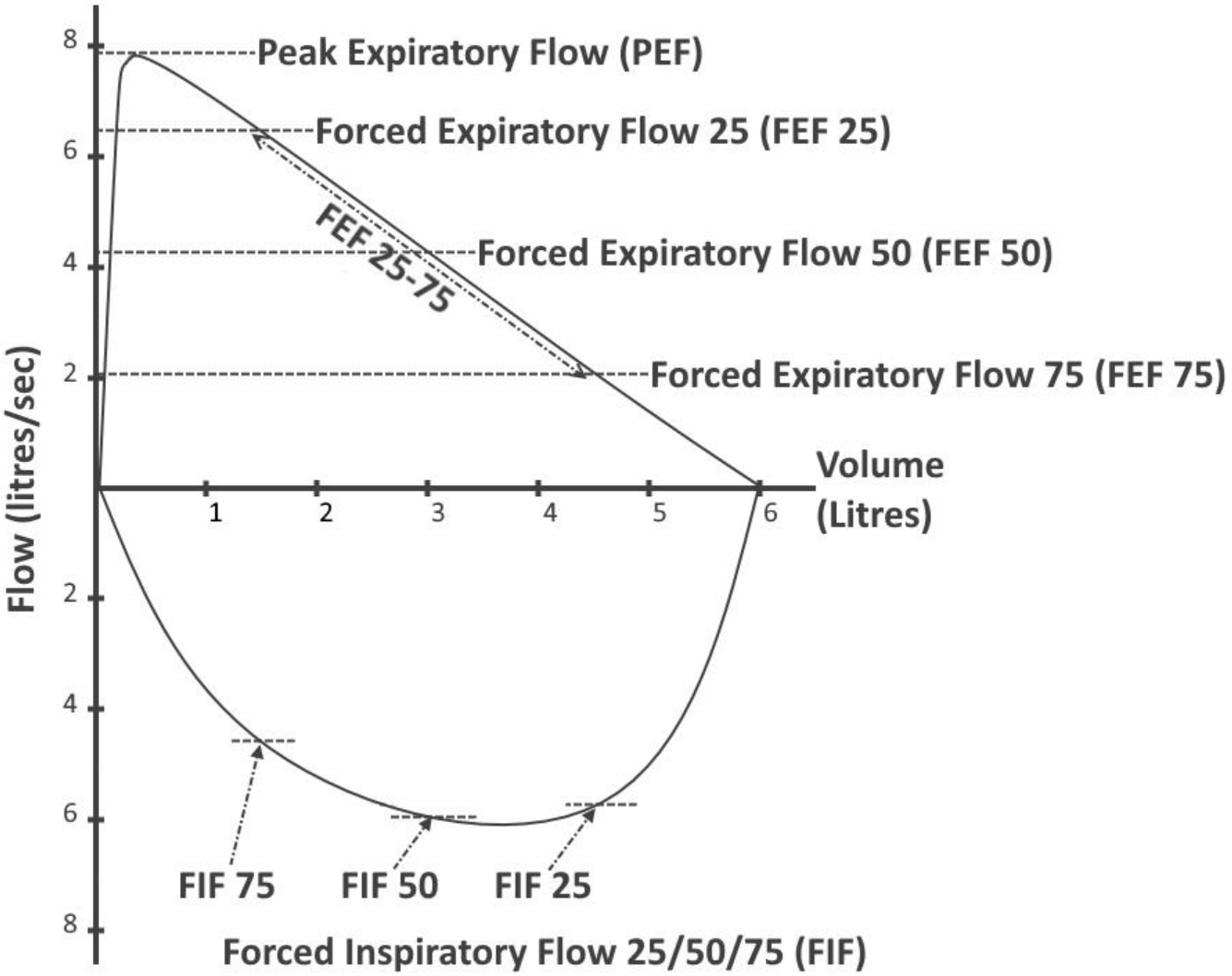
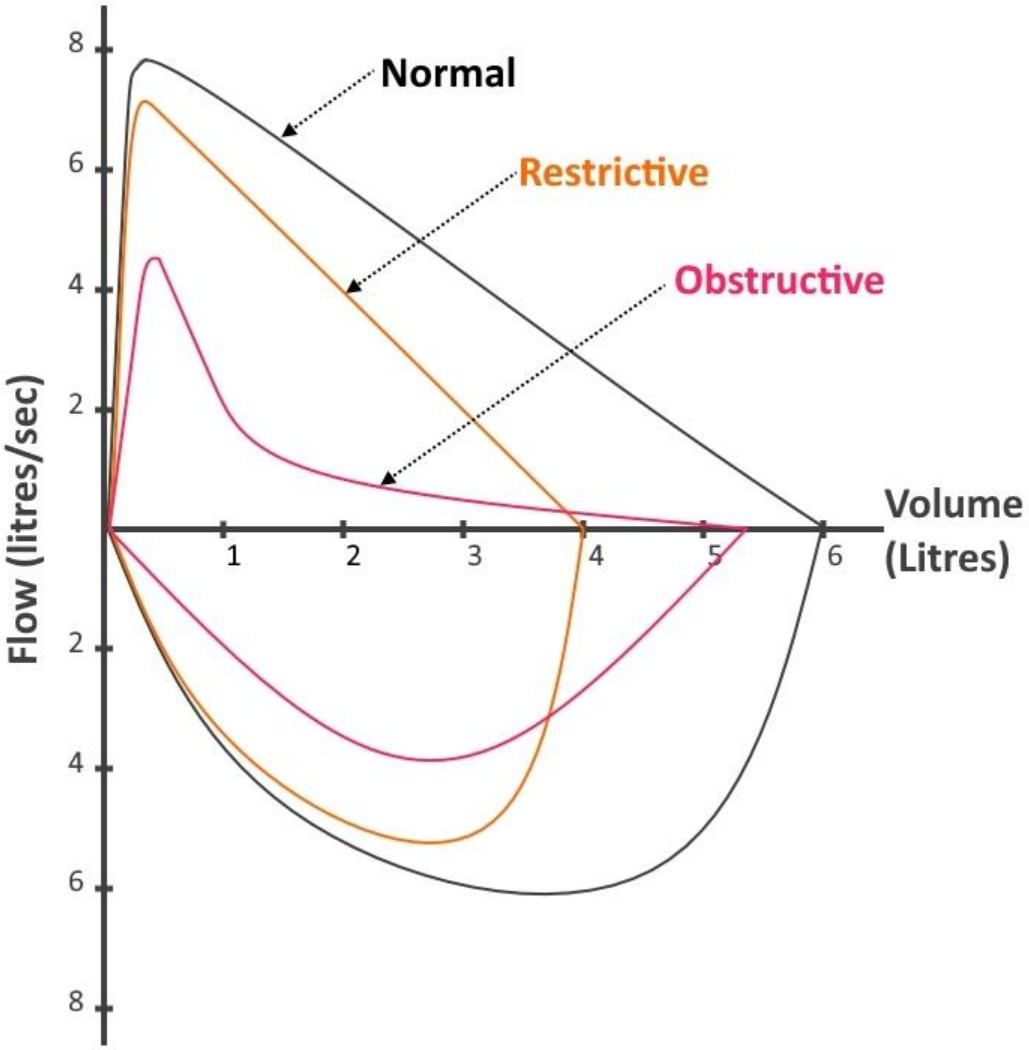


FIGURE 390-3 High-resolution computed tomography scan of chest demonstrating patchy reticular nodularity, including areas of confluence.

Normal Flow Volume Loop



Flow Loop Patterns



Normal Pattern:

PEF Normal
Pattern Initially rapid, decreasing steadily
Volume Normal

Restrictive Pattern:

PEF Normal or slightly Reduced
Pattern Normal
Volume Reduced

Obstructive Pattern:

PEF Reduced
Pattern Concave
Volume Normal or Reduced

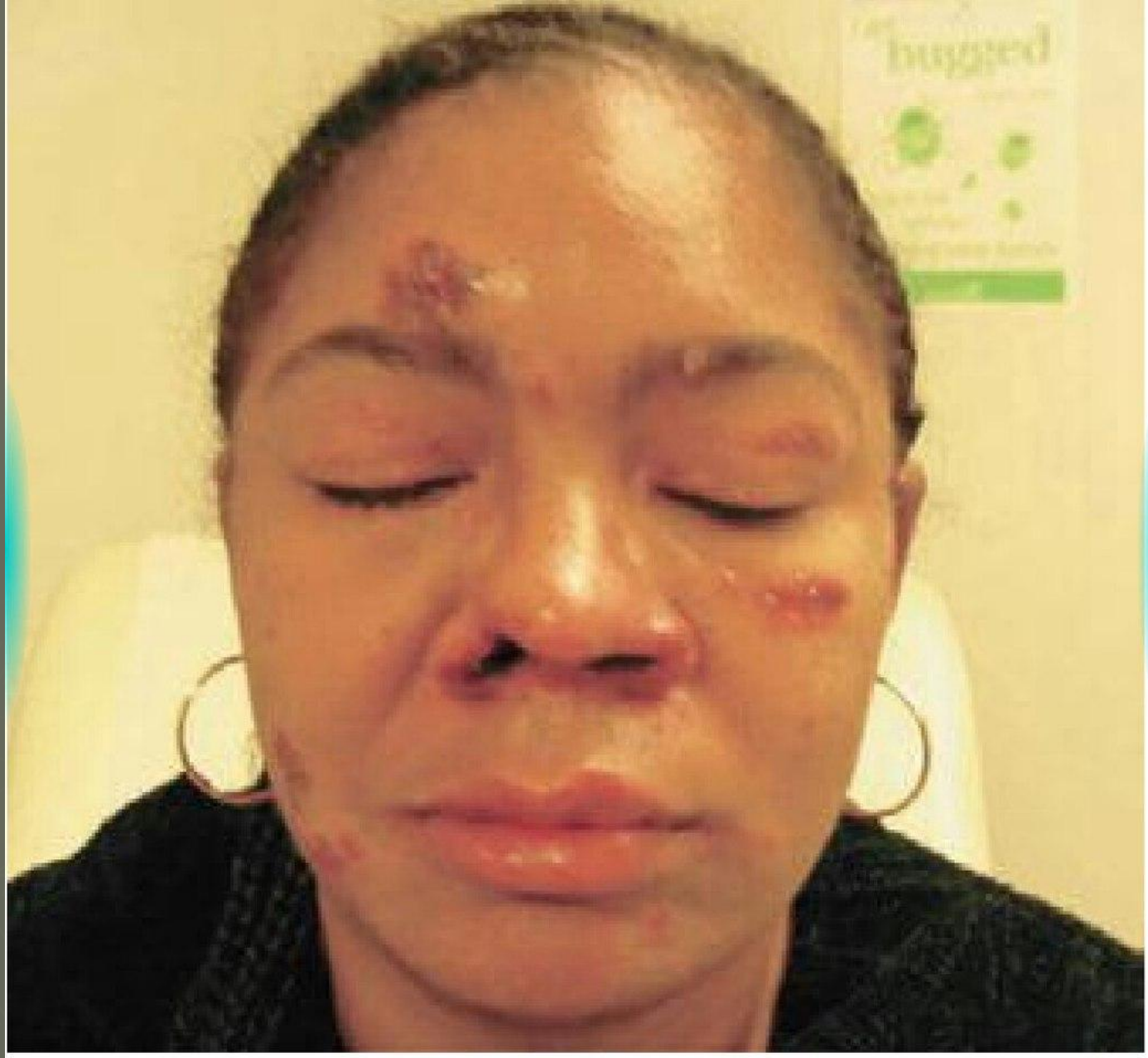


FIGURE 390-4 **Chronic inflammatory lesions** around nose, eyes, and cheeks, referred to as lupus pernio.

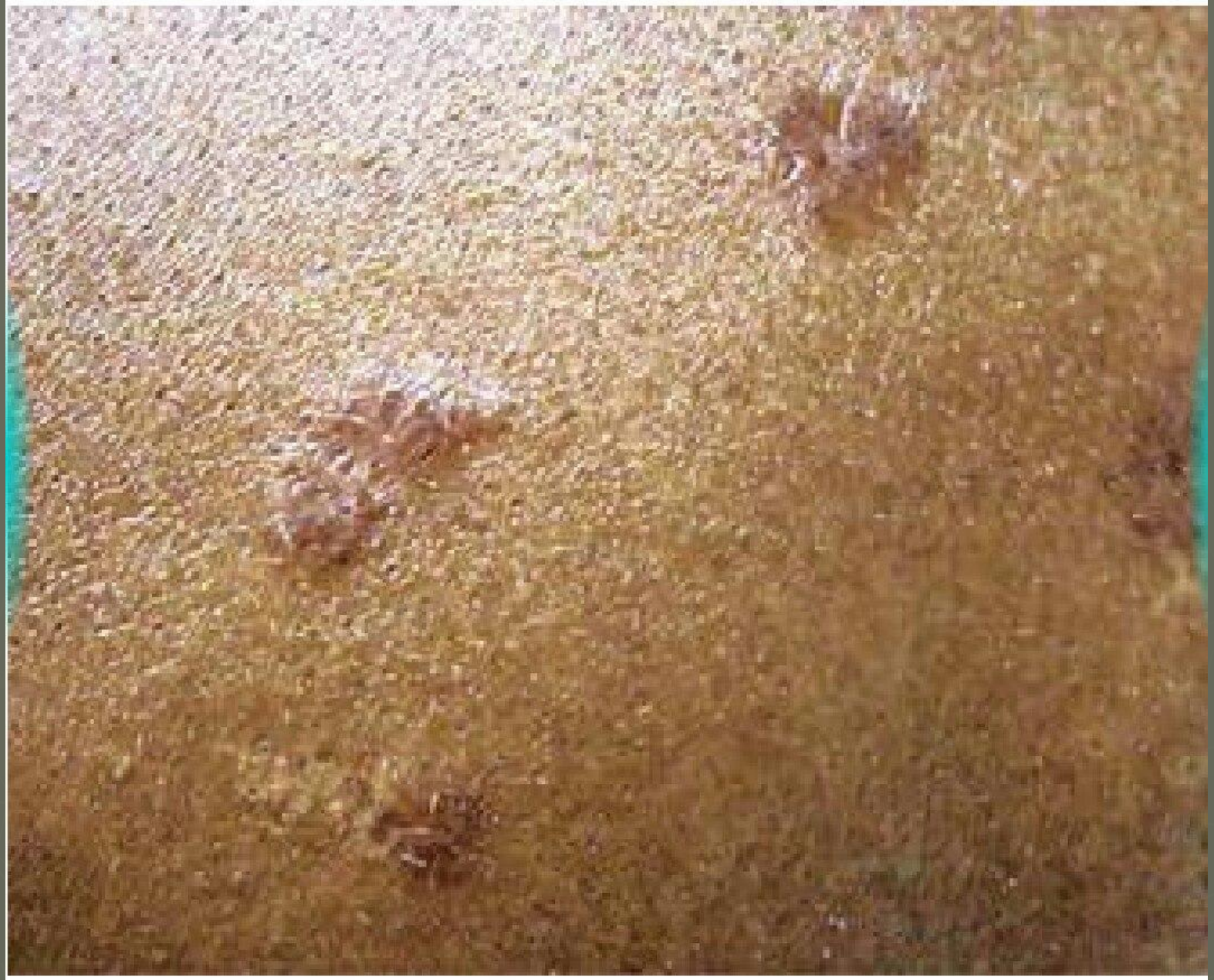


FIGURE 390-5 **Maculopapular lesions on the trunk** of a sarcoidosis patient.

Table 2 | Special clinical challenges in sarcoidosis

Manifestation	Assessment	Treatment	Major unresolved issues
Cardiac sarcoidosis	Echocardiogram, Holter monitor, cardiac MRI or PET, electrophysiology study	Corticosteroids, steroid-sparing drugs, heart failure therapy (for example, afterload reducing agents, diuretics, β-blockers), antiarrhythmic drugs, pacemaker and/or ICD	Risk stratification for ICD
Neurosarcoidosis	Brain MRI, lumbar puncture, nerve conduction study	Corticosteroids, steroid-sparing drugs, antiseizure therapy	Establishment of diagnostic criteria that do not require neurologic biopsy
Pulmonary hypertension	Echocardiogram, right heart catheterization	Corticosteroids, steroid-sparing drugs	Indications for vasodilator therapy
Small fiber neuropathy	Skin biopsy, sensorineural testing	Neuropathic pain therapy	Role of TNF inhibitors

Abbreviation: ICD, implantable cardiac defibrillator; TNF, tumor necrosis factor.

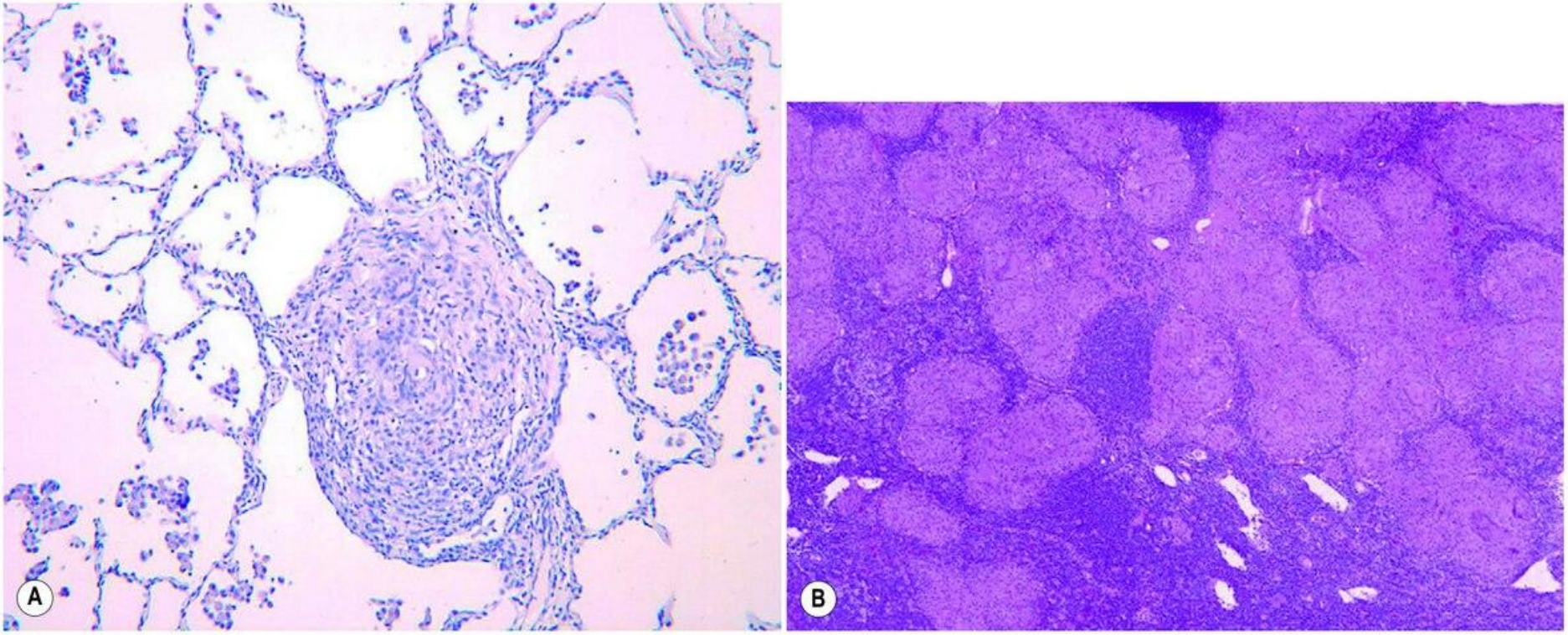


Fig. 72.1 (A) Open lung biopsy showing typical noncaseating epithelioid granuloma, giant cells, and lymphocytic infiltrates in lung parenchyma in sarcoidosis. (B) Lymph node biopsy showing extensive replacement with well-defined epithelioid granulomas in a patient with sarcoidosis.

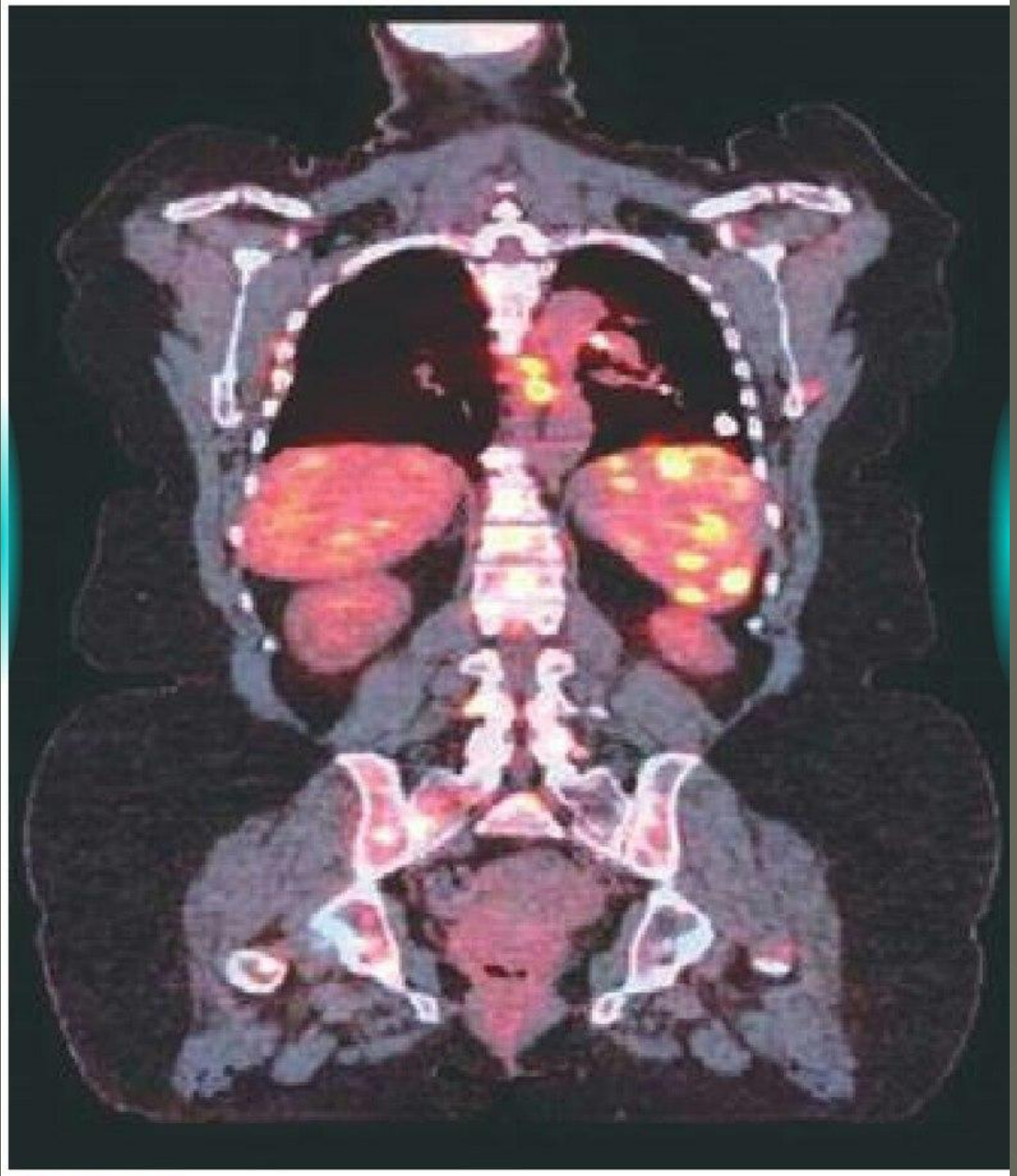


FIGURE 390-7 Positron emission tomography and computed tomography scan merged demonstrating increased activity in spleen, ribs, and spine of patient with sarcoidosis.

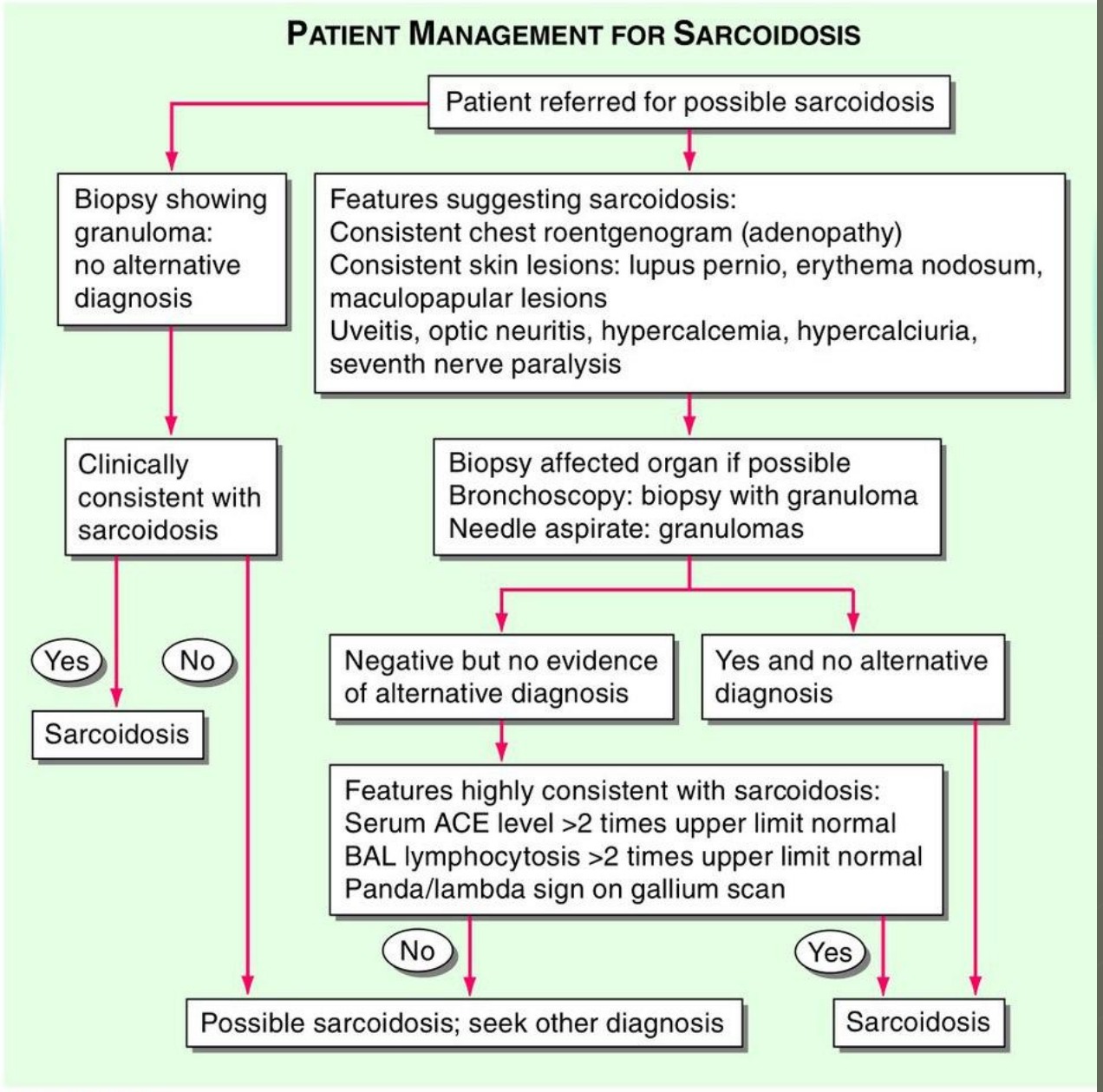
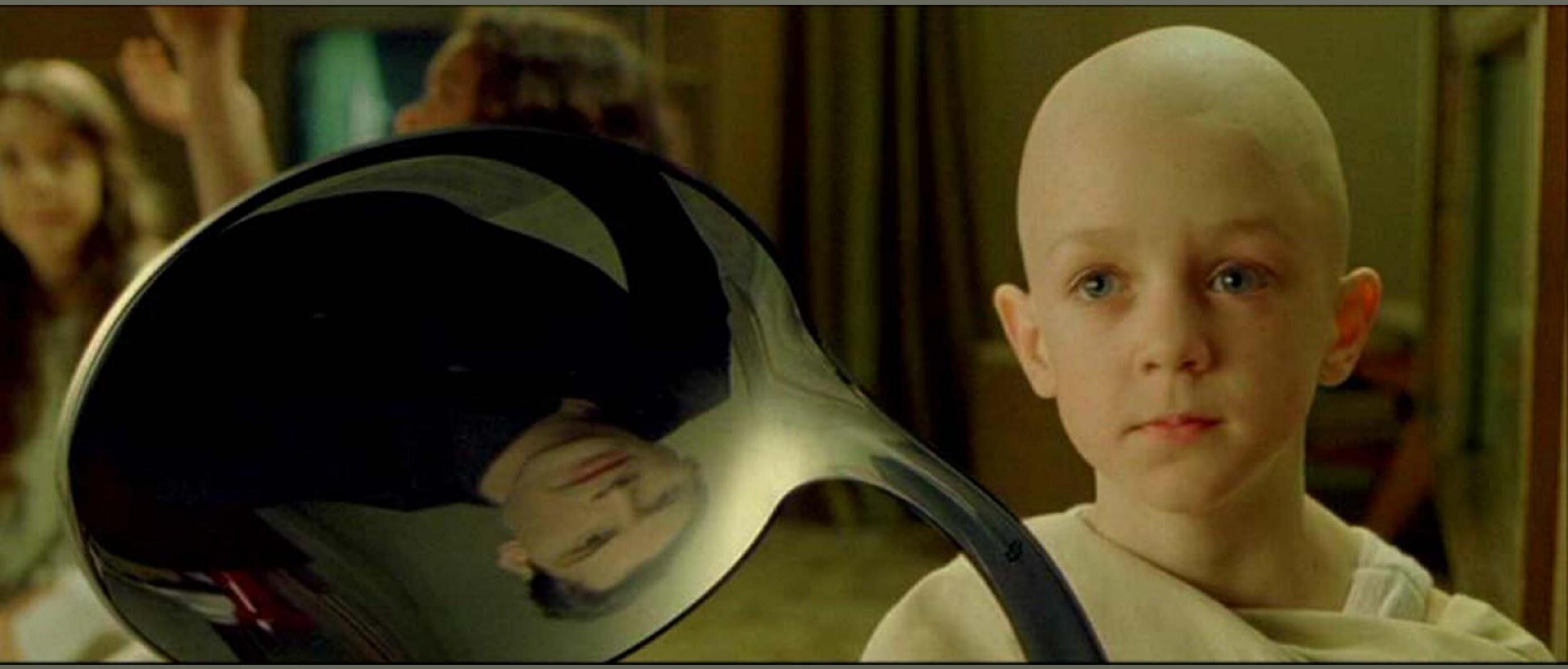


FIGURE 390-8 Proposed approach to management of patient with possible sarcoidosis. Presence of one or more of these features supports the diagnosis of sarcoidosis: uveitis, optic neuritis, hypercalcemia, hypercalciuria, seventh cranial nerve paralysis, diabetes insipidus. ACE, angiotensin-converting enzyme; BAL, bronchoalveolar lavage.



Box 2 | Consensus approach to treatment of sarcoidosis

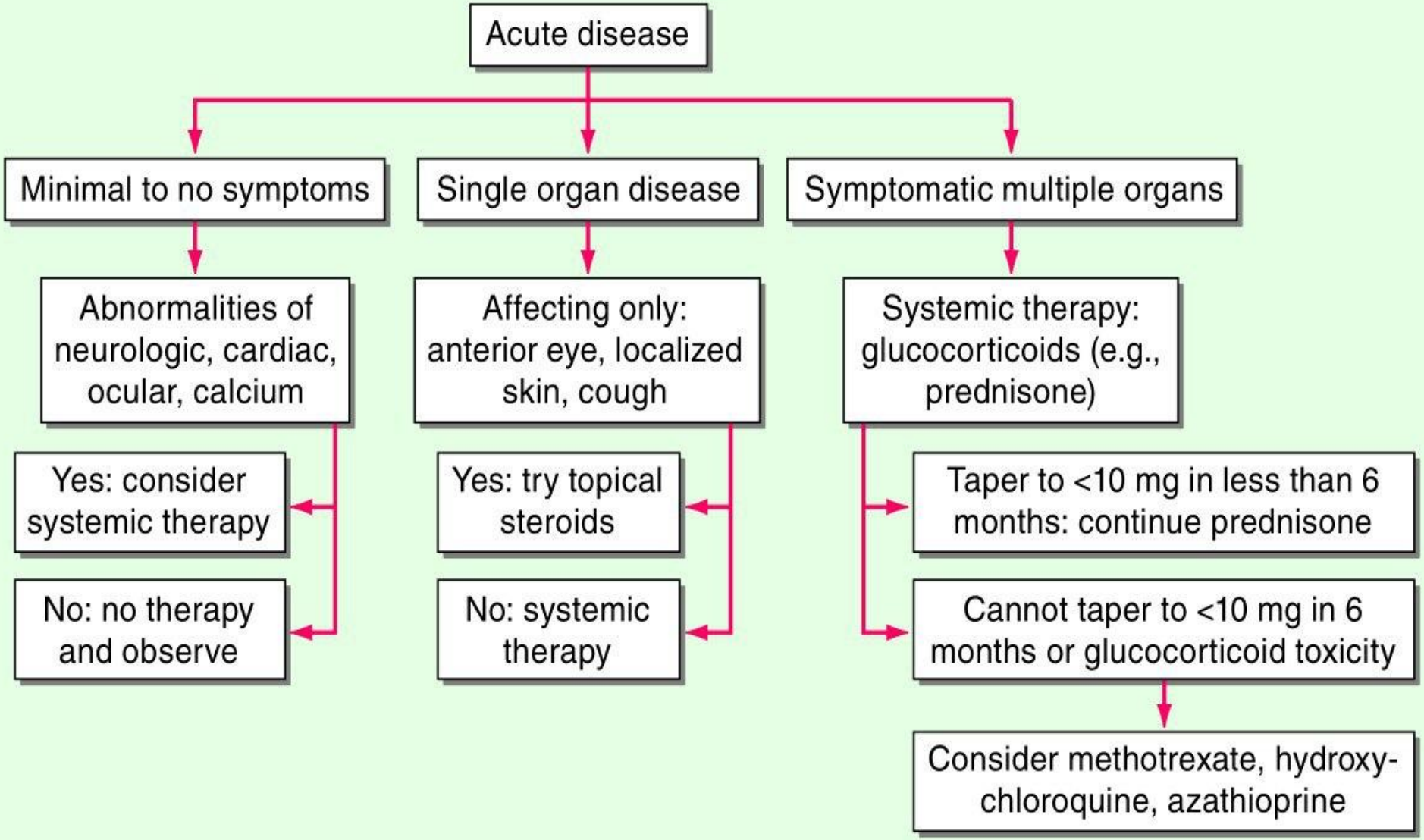
1. Treatment is not indicated for an asymptomatic patient with only lymphadenopathy
2. Treatment is not indicated in an asymptomatic patient with pulmonary infiltrates and mildly abnormal lung function and stable disease
3. Oral corticosteroids are the first line of therapy in patients with progressive disease as determined by radiology or lung function, presence of specific symptoms (including dyspnea, cough or other chest symptoms) or extrapulmonary disease
4. Treatment with prednisone (or equivalent), at a dose of 20–40 mg per day initially for 4 weeks and then reduced to a maintenance dose which will control symptoms and disease progression for a period of 6–24 months
5. Bisphosphonates are recommended to minimize steroid-induced osteoporosis
6. Inhaled corticosteroids are not beneficial as initial treatment or for maintenance therapy. However, inhaled corticosteroids could be considered for symptom control (cough) or bronchial hyper-reactivity in a subgroup of patients
7. Steroid-sparing immunosuppressive or anti-inflammatory treatments have an undefined role in sarcoidosis, but should be considered in patients when corticosteroids are not controlling the disease or side effects are intolerable. At present, methotrexate is the treatment of choice. Azathioprine is often used when methotrexate is contraindicated or not tolerated*
8. Lung (and heart)* transplantation should be considered in end-stage pulmonary and cardiac sarcoidosis

Adapted from joint guidelines from the British Thoracic Society, the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society.[95] *Author changes consistent with other consensus statements.[1]

Indications for corticosteroid therapy in patients with sarcoidosis

- Pulmonary involvement
  - Moderate or severe, symptomatic pulmonary disease
  - Progressive, symptomatic pulmonary disease
  - Persistent pulmonary infiltrates or abnormal lung function for 1–2 years with mild symptoms to assess reversibility
  - Advanced fibrocystic disease
- Extrapulmonary involvement
  - Threatened organ failure: severe ocular, cardiac, or CNS disease
  - Posterior uveitis or anterior uveitis not responding to local steroids
  - Persistent hypercalcemia
  - Persistent renal or hepatic dysfunction
  - Pituitary disease
  - Myopathy
  - Palpable splenomegaly or evidence of hypersplenism such as thrombocytopenia
  - Severe fatigue and weight loss
  - Painful lymphadenopathy
  - Disfiguring skin disease

Algorithm for Management of Sarcoidosis



Management Algorithm of Chronic Disease

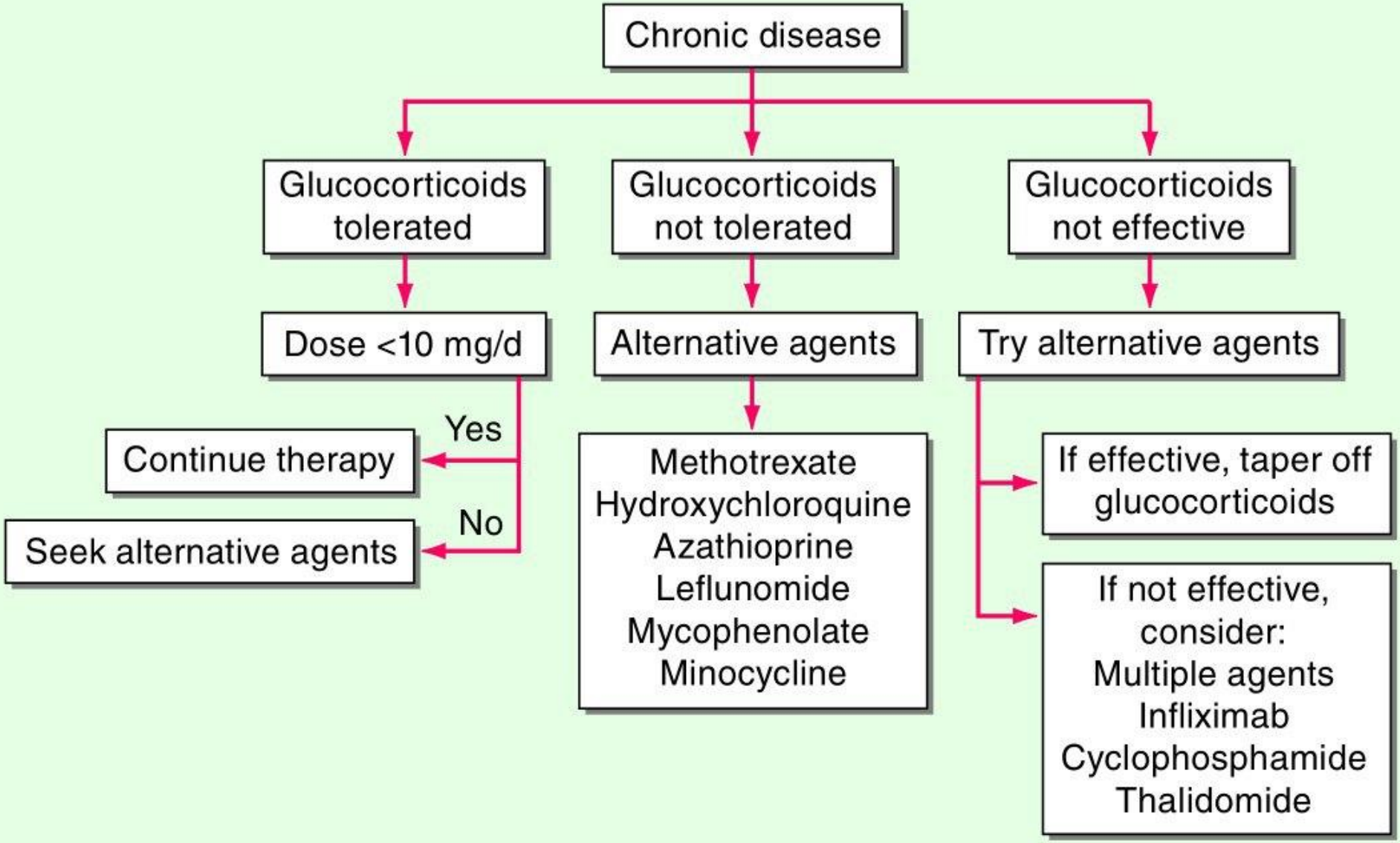


TABLE 390-2 COMMONLY USED DRUGS TO TREAT SARCOIDOSIS

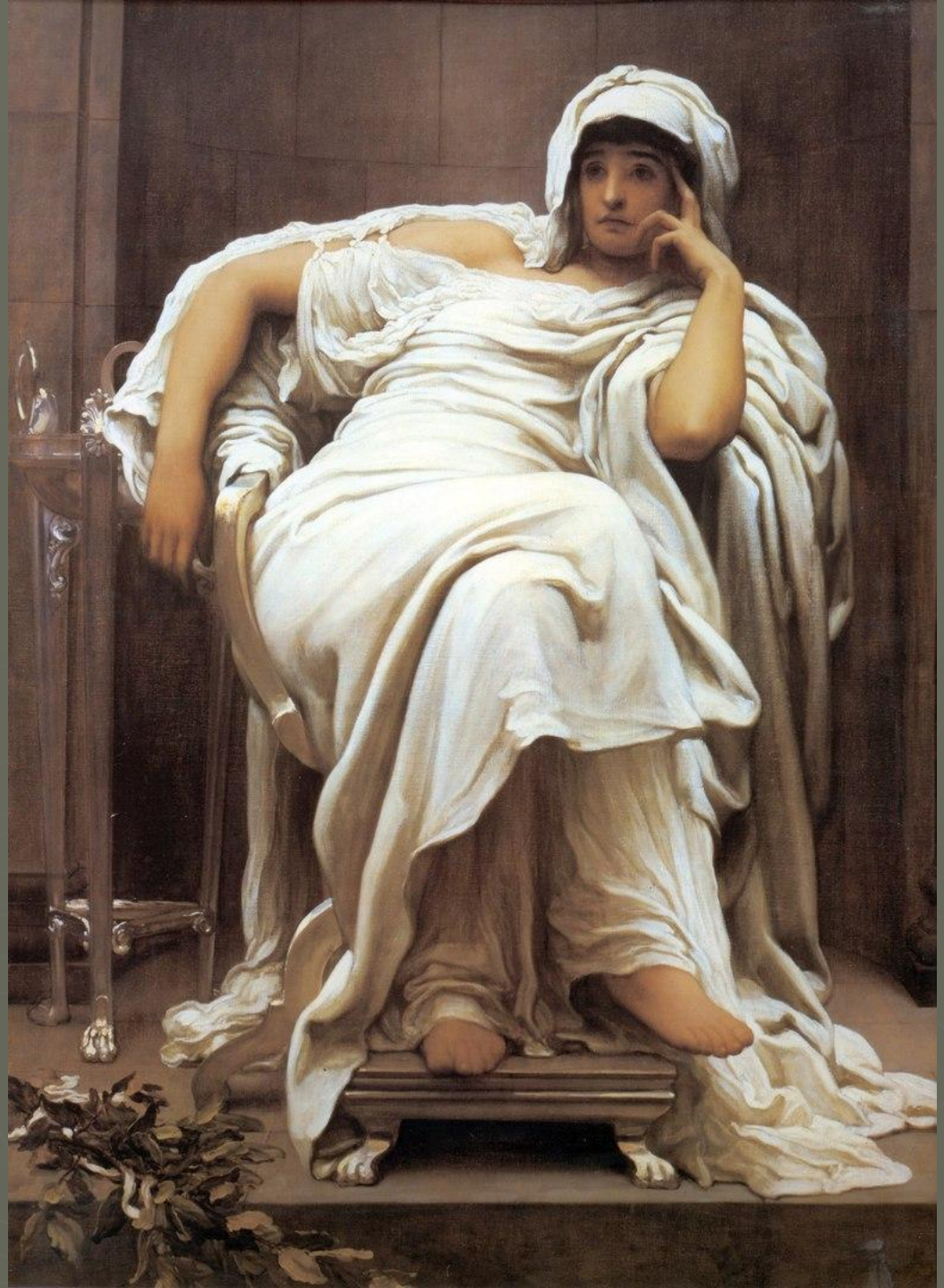
Drug	Initial Dose	Maintenance Dose	Monitoring	Toxicity	Support Therapy[a]	Support Monitoring[a]
Prednisone	20–40 mg qd	Taper to 5–10 mg	Glucose, blood pressure, bone density	Diabetes, osteoporosis	A: Acute pulmonary D: Extrapulmonary	
Hydroxychloroquine	200–400 mg qd	400 mg qd	Eye exam q6–12 mo	Ocular	B: Some forms of disease	D: Routine eye exam
Methotrexate	10 mg qwk	2.5–15 mg qwk	CBC, renal, hepatic q2mo	Hematologic, nausea, hepatic, pulmonary	B: Steroid sparing C: Some forms chronic disease	D: Routine hematologic, renal, and hepatic monitoring
Azathioprine	50–150 mg qd	50–200 mg qd	CBC, renal q2mo	Hematologic, nausea	C: Some forms chronic disease	D: Routine hematologic monitoring
Infliximab	3–5 mg/kg q2wk for 2 doses	3–10 mg/kg q4–8 wk	Initial PPD	Infections, allergic reaction, carcinogen	A: Chronic pulmonary disease	B: Caution in patients with latent tuberculosis or advanced congestive heart failure

[a]Grade A: supported by at least two double-blind randomized control trials; grade B: supported by prospective cohort studies; grade C: supported primarily by two or more retrospective studies; grade D: only one retrospective study or based on experience in other diseases.

Abbreviations: CBC, complete blood count; PPD, purified protein derivative test for tuberculosis.

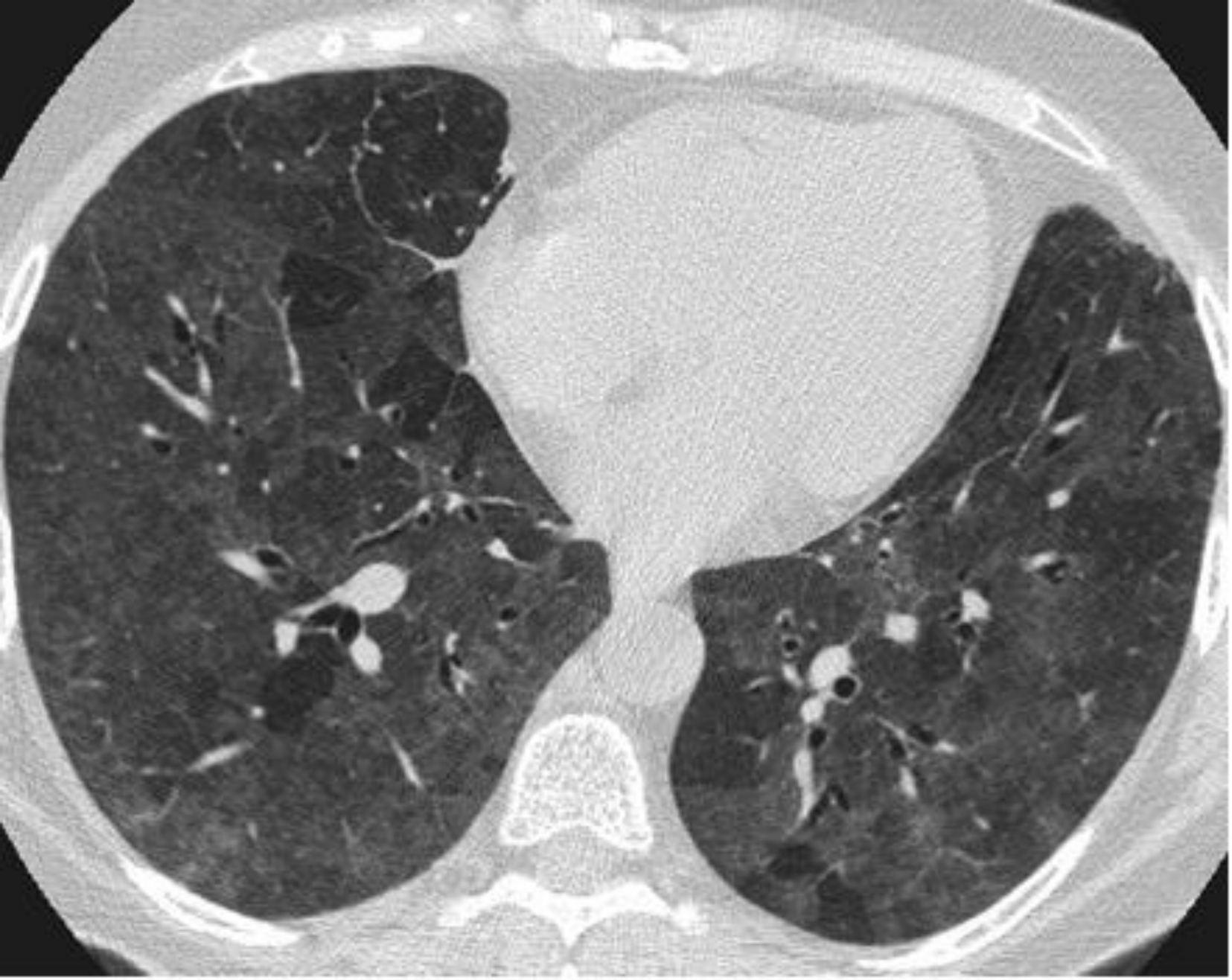
Clinical Relevance

- Multisystem disease with heterogeneous manifestations dependent on location and extent of granulomatous inflammation
  - Pulmonary involvement $>90\%$
- Diagnosis based on consistent manifestations and biopsy showing typical pathology
  - No useful biomarkers for diagnosis or prognosis
- Association with Th1-promoting biologics (e.g., INF-α) and immune reconstitution in HIV patients undergoing HAART therapy supports the concept of sarcoidosis as a Th1-mediated disorder
- Treatment involves non-specific anti-inflammatory or immunosuppressive therapies
  - Clinical trials needed to establish roles of individual therapies
  - Benefit of anti-TNF therapies point to a central role for TNF in sarcoidosis



Клиническая задача

- *Областная клиническая больница г.Саратов*
- Больной П., 58 лет, в апреле 2013г поступил в отделение пульмонологии ОКБ г. Саратова с жалобами на одышку смешанного характера при незначительной физической нагрузке, малопродуктивный кашель с отделением небольшого количества светло-коричневой мокроты, перебои в работе сердца. Пациент на протяжении 5 лет страдает мерцательной аритмией, постоянной терапии не получает. За 10 дней до госпитализации у больного появилось сердцебиение (пульс 120-130 уд. в мин со слов больного), за медицинской помощью не обращался, самостоятельно начал принимать кордарон (суточная доза 1200 мг), на фоне чего тахикардия прекратилась. Через 5-6 дней после начала приема препарата появилась выраженная одышка в покое, периодически непродуктивный кашель. Одышка постепенно прогрессировала, появилась мокрота, температура тела не повышалась. При поступлении: состояние средней тяжести, ЧДД 21-22 в мин, одышка смешанного характера при незначительной физической нагрузке, аускультативно-дыхание жесткое, базальная крепитация с двух сторон. Мерцательная аритмия с ЧСС 68 уд в мин. При КТ-легких были выявлены изменения по типу «матового стекла», при спирографии- нарушения ФВД по смешанному типу: ЖЕЛ-61%, ФЖЕЛ-55%, ОФВ1-59%, ОФВ1/ФЖЕЛ-85%,СРБ-24 мг/л, оксигенация крови 96% в покое, при нагрузке 84-85%. С учетом анамнеза заболевания и выявленных изменений в легких было установлено наличие интерстициальной пневмонии. Учитывая наличие «матового стекла», повышения СРБ, была проведена пульс-терапия преднизолоном 510 мг № 3, назначен преднизолон per os 20 мг/сут. На фоне терапии наблюдалось уменьшение выраженности одышки, отсутствие кашля, при аускультации крепитация в меньшем объеме. Больной выписан в удовлетворительном состоянии, в качестве альтернативной антиаритмической терапии назначен бисопролол. Данное наблюдение представляет интерес вследствие трудности диагностики заболевания, из-за отсутствия специфических клинических и морфологических проявлений.




the cake is a lie.
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Благодарю за внимание