



СЕЧЕНОВСКИЙ УНИВЕРСИТЕТ  
НАУК О ЖИЗНИ

# Panniculitis as a manifestation of metal-associated Autoimmune/Inflammatory Syndrome Induced by Adjuvants

a case-based review

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# Introduction & History

- Autoimmune/inflammatory syndrome induced by adjuvant (ASIA), also known as Shoenfeld's syndrome, incorporates *specific* and *non-specific* autoimmune conditions.
- ASIA encompasses conditions linked to previous exposure to an adjuvant substance.

# Suggested criteria for ASIA diagnosis

## Major criteria

Exposure to external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestation

The appearance of "typical" clinical manifestations

- Myalgia, myositis, or muscle weakness
- Arthralgia, and/or arthritis
- Chronic fatigue, unrefreshing sleep, or sleep disturbances
- Neurological manifestations (especially associated to demyelination)
- Cognitive impairment, memory loss
- Pyrexia, dry mouth

Removal of inciting agent induces improvement

Typical biopsy of involved organs

## Minor criteria

The appearance of autoantibodies directed at the suspected adjuvant

Other clinical manifestations (i.e. irritable bowel syndrome)

Specific HLA (i.e. HLA DRB1, HLA DQB1)

Evolution of an autoimmune disease (i.e. multiple sclerosis, systemic sclerosis)

- There must be the presence of at least two major OR
- One major and two minor criteria

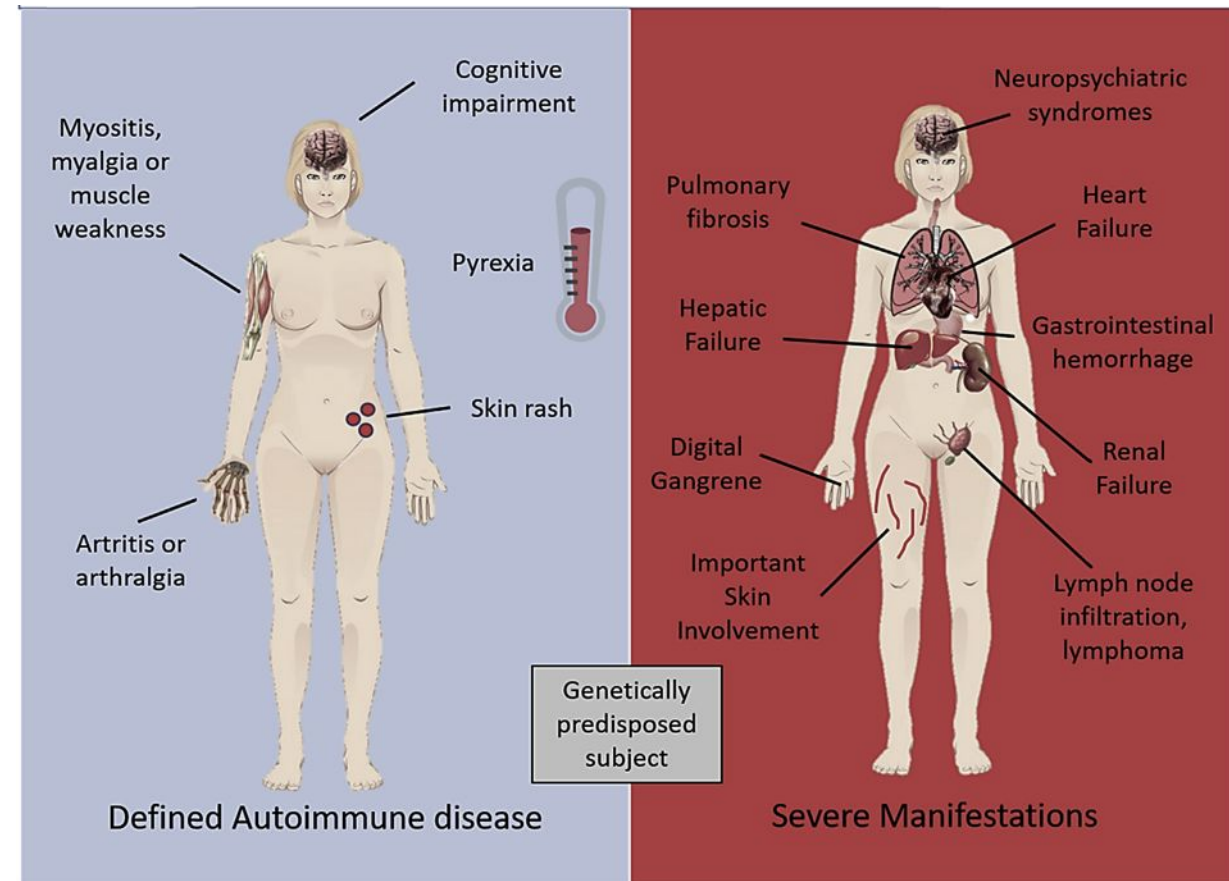


Fig. ASIA clinical spectrum from defined autoimmune disease to severe manifestations

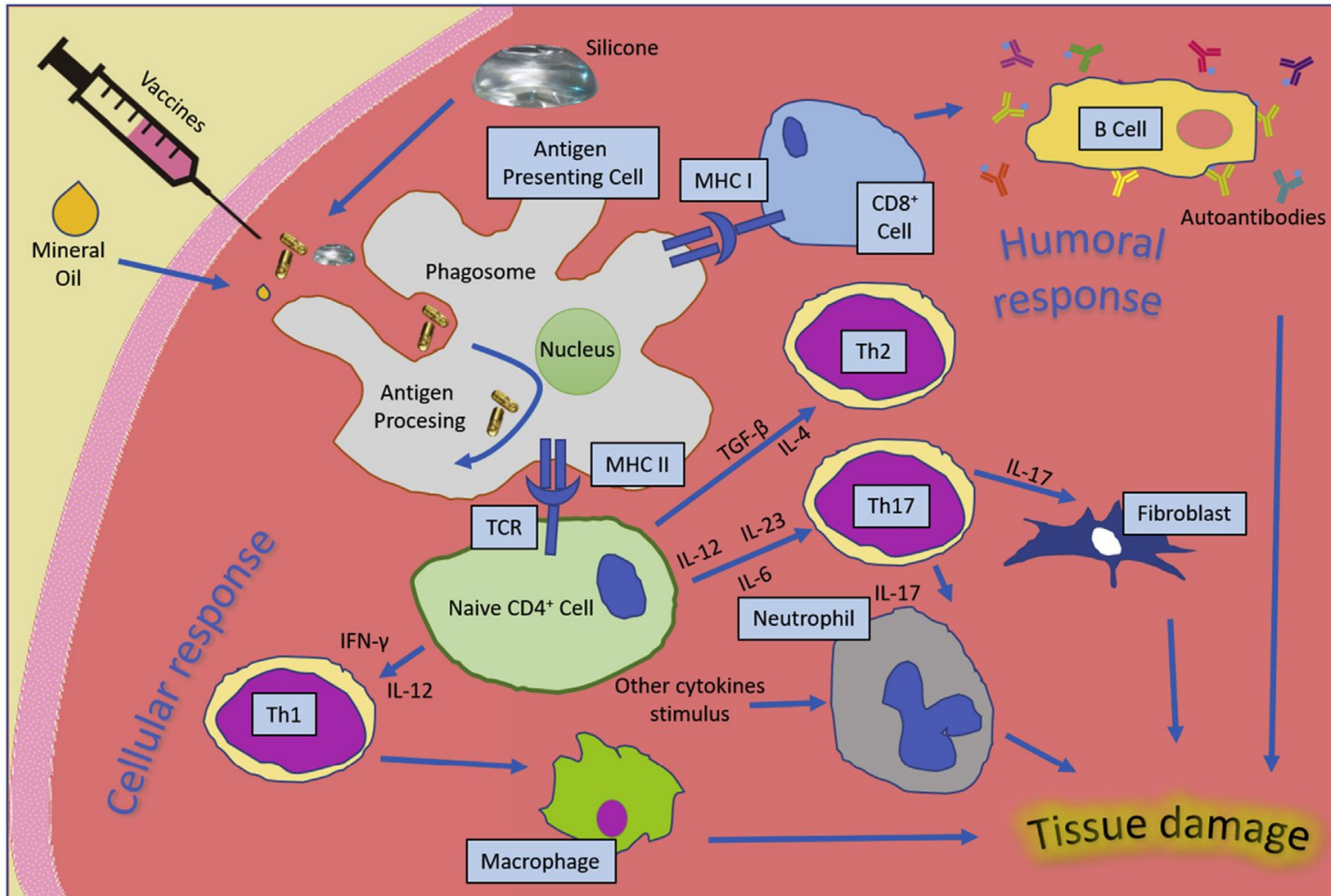
# Adjuvants

- Silicone
- Hyaluronic acid
- Filler substances, especially acrylamides and methacrylate
- Aluminium and mercury containing vaccines (commonly, HBV, HPV and H1N1 vaccines)
- Diverse metals and metal alloys (nickel, chrome, cobalt, titanium)





# Suspected mechanism of adjuvant-induced autoimmunity.



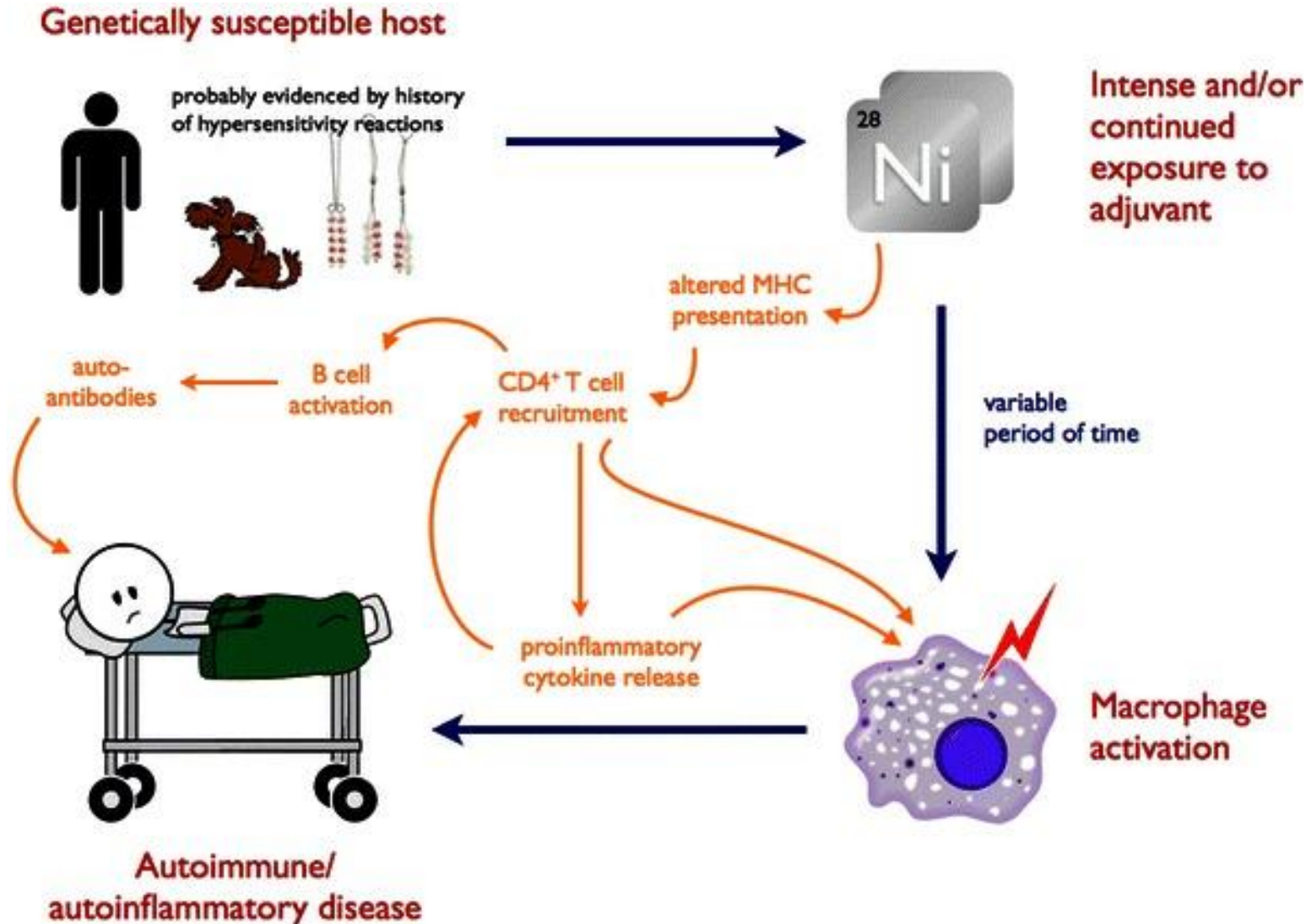
## Suspected mechanisms of adjuvants-induced autoimmunity

- Alteration of the host's immune system
- Polyclonal activation of B cells
- Effects on cellular immunity
- Effects on immune regulatory cells
- Effects on viral induced antibodies
- Molecular mimicry
- Bystander activation
- Epitope spreading
- Anti-idiotypic network
- Changing the host's antigens
- Expression of HLA\* family antigens
- Modification of surface antigens
- Induction of novel antigens
- Interaction with Toll-like receptors (TLRs)
- Antigens translocation
- Release of inflammatory cytokines

\*HLA: Human leukocyte antigen.

Perricone C et al. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the pathogenic, clinical and diagnostic aspects.  
 Jara LJ et al (2019) Autoimmune/Inflammatory Syndrome Induced by Adjuvants (Shoenfeld's Syndrome).

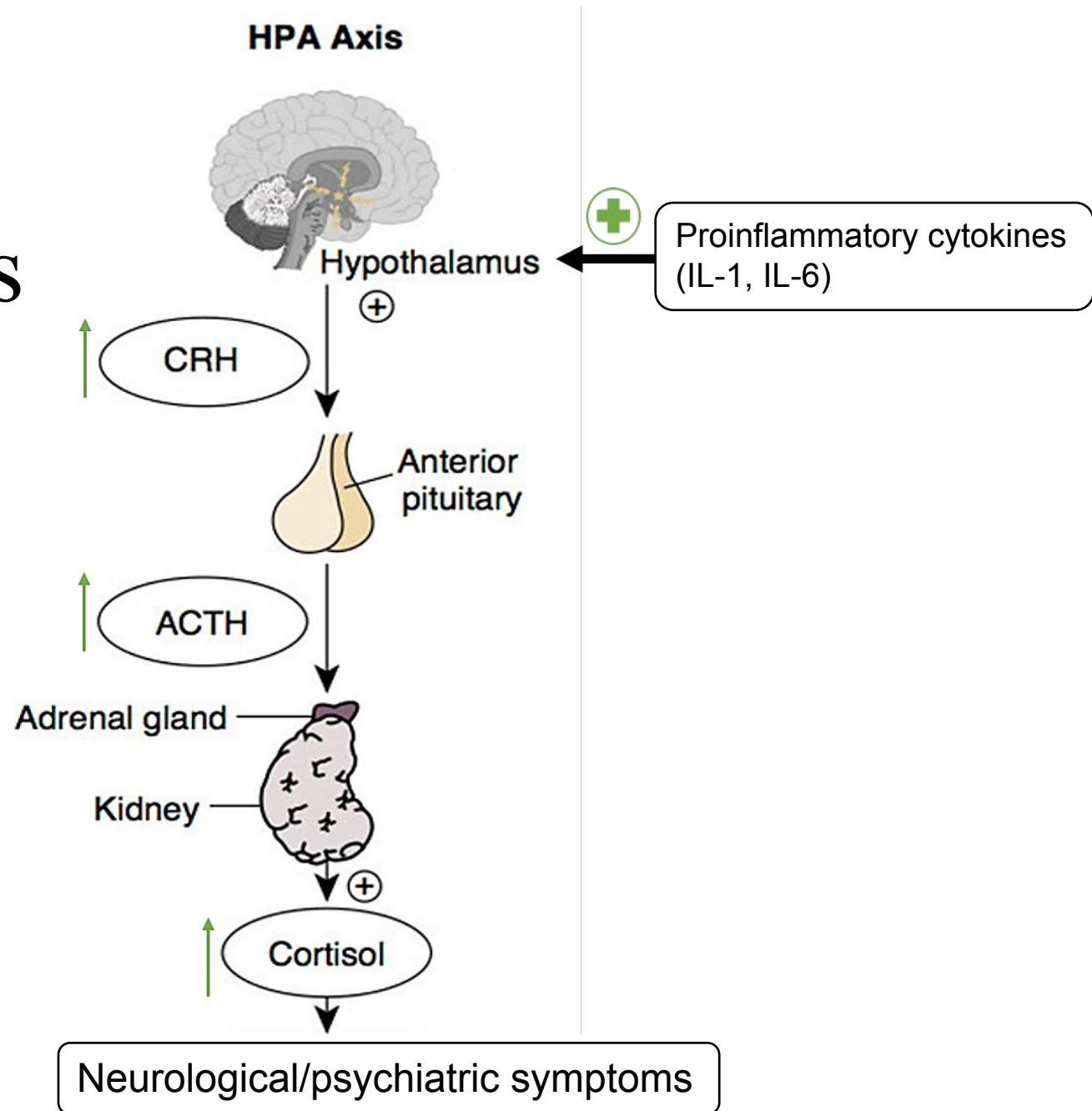
# Pathogenetic mechanisms of nickel-associated autoimmunity



Amplification of the immune response. Persistent exposition to nickel ions or its derivatives is capable of (1) macrophage activation and (2) antigen presentation in the context of MHC class II molecules to CD4<sup>+</sup> T cells.

# Pathogenetic mechanisms of neurological symptoms

- IL-1 and IL-6 are able to activate the HPA axis at the central level by directly stimulating the hypothalamic secretion of CRH. Based on this evidence, and considering that the acute administration of cytokines may reproduce many of the symptoms of depression, cognitive impairment, memory, nonrestful sleeps, or sleep disturbances.



# *Specific ASIA-associated conditions*

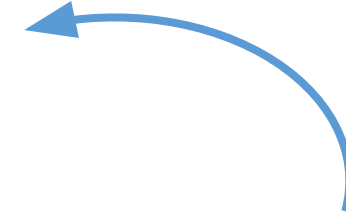
Siliconosis

Gulf War syndrome

Macrophagic myofasciitis syndrome

Sick building syndrome

Post-vaccination syndrome

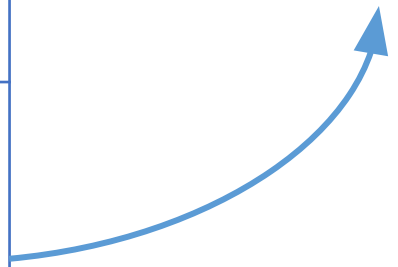




# *Non-specific* ASIA-associated conditions

The Wide Spectrum of Diseases Associated to Autoimmune/Inflammatory Syndrome Induced by Adjuvants	
<b>Neurologic manifestations</b>	Acute disseminated encephalomyelitis, Guillain-Barré syndrome, multiple sclerosis, narcolepsy, transverse myelitis, inflammatory polyradiculopathy, memory loss, peripheral neuropathy, epilepsy, cerebral vascular disease
<b>Well-defined rheumatic diseases</b>	Mixed connective tissue disease, Sjogren's syndrome, dermatomyositis, systemic sclerosis, giant cell arteritis, polyarteritis nodosa, inflammatory myopathy, Still's disease, Kawasaki disease, severe cutaneous small-vessel vasculitis, fibromyalgia, psoriatic arthritis
<b>Gastroenterologic manifestations</b>	Inflammatory bowel disease, primary biliary cirrhosis, autoimmune hepatitis, antiphospholipid syndrome, ulcerative colitis, Crohn's disease, pancreatitis
<b>Endocrine manifestations</b>	Hashimoto thyroiditis, subacute thyroiditis, primary ovarian failure
<b>Hematologic manifestations</b>	Hemolytic anemia, autoimmune thrombocytopenia, pseudolymphoma, lymphoma
<b>Renal manifestations</b>	Chronic kidney disease
<b>Psychiatric manifestations</b>	Depression, obsessive compulsive disorder, sleep disorders
<b>Cardiac manifestations</b>	Postural orthostatic tachycardia, myocarditis, pericarditis
<b>Other</b>	Sarcoidosis, sicca syndrome, angioedema

**Panniculitis?**



Alijotas-Reig J (2015) Human adjuvant-related syndrome or autoimmune/inflammatory syndrome induced by adjuvants. Where have we come from? Where are we going? A proposal for new diagnostic criteria.

Jara LJ et al (2019) Autoimmune/Inflammatory Syndrome Induced by Adjuvants (Shoenfeld's Syndrome).

# Introduction

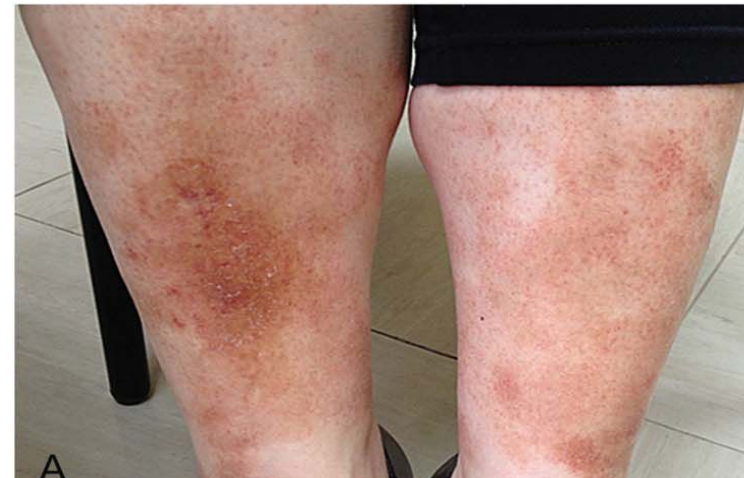
- Panniculitis encompasses a heterogeneous group of diseases characterized by lesions of the subcutaneous and mesenteric fat and the involvement of multiple organs and systems into the pathological process.



Subcutaneous fat necrosis of the newborn



Erythema nodosum



Lipodermatosclerosis



Eosinophilic panniculitis

Ter Poorten MC, Thiers BH (2002) Panniculitis.

Wick MR (2017) Panniculitis: A summary.

Llamas Velasco M (2018) Clues in Histopathological Diagnosis of Panniculitis.

# Classification of the panniculitides

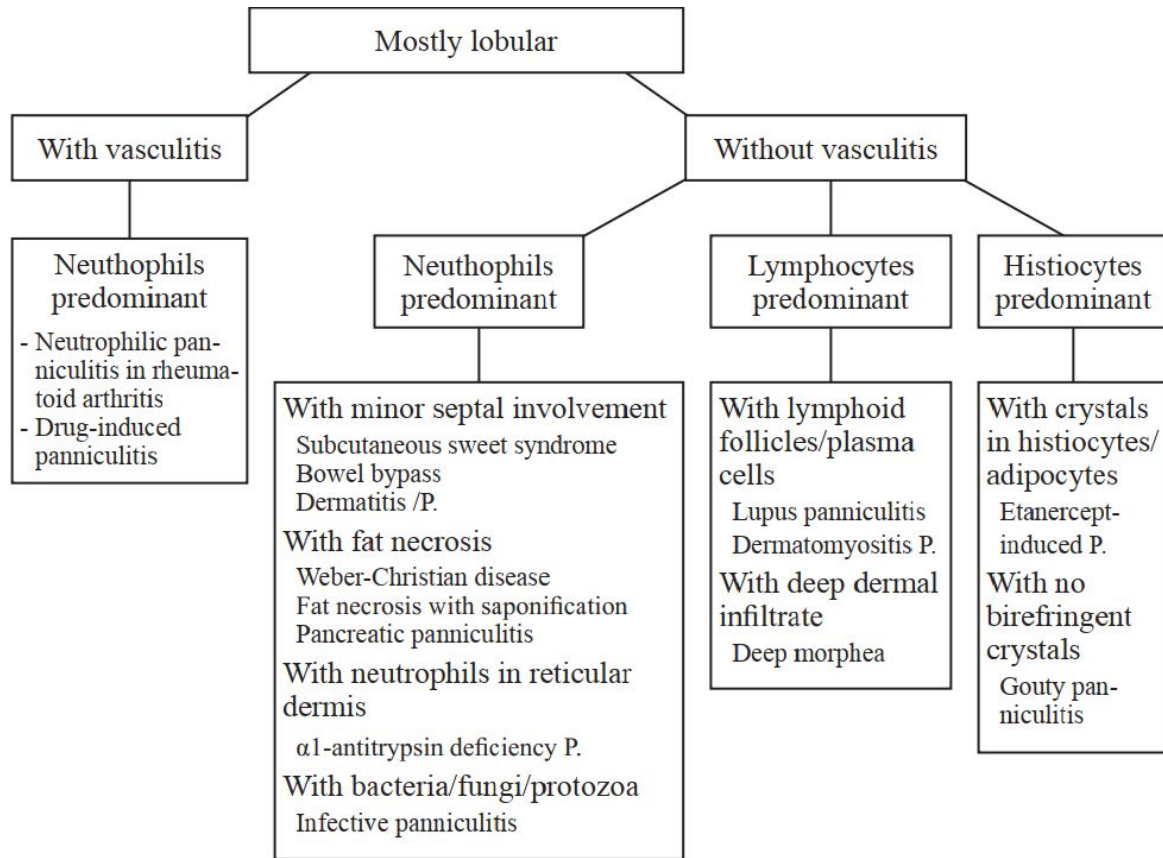


Fig. Algorithm for the diagnosis of predominantly-lobular panniculitides

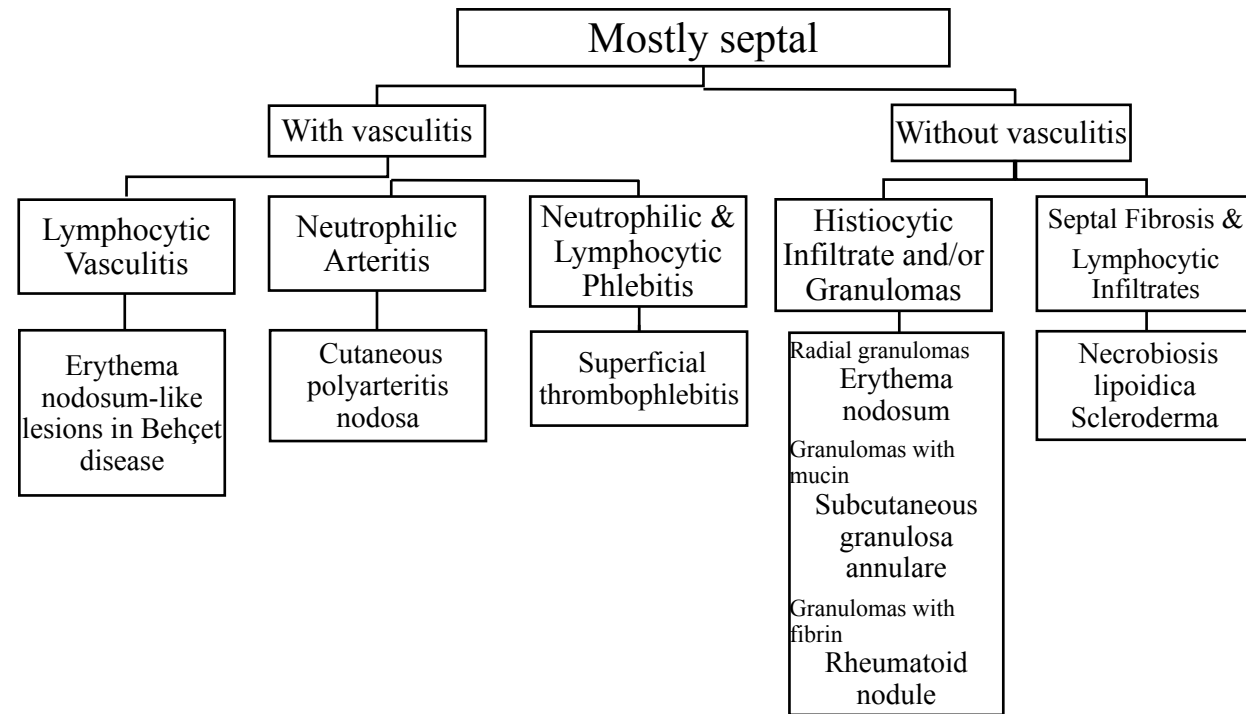


Fig. Algorithm for the diagnosis of predominantly-septal panniculitides

1. Septal or Lobular
2. Vasculitis: +/-
3. Composition of the inflammatory infiltrate

# Physician office visit

Chills, pharyngalgia

Fever

Dyspnea, chest tightness,  
persistent cough

Polyarthralgia, (poly)arthritis

Scars on the skin of upper /  
lower extremities & trunk

Myalgia, weight loss

Diarrhea, fatigue,  
decreased appetite



Inflammatory  
skin lesions  
of the upper,  
lower  
extremities &  
trunk



Phlebologist

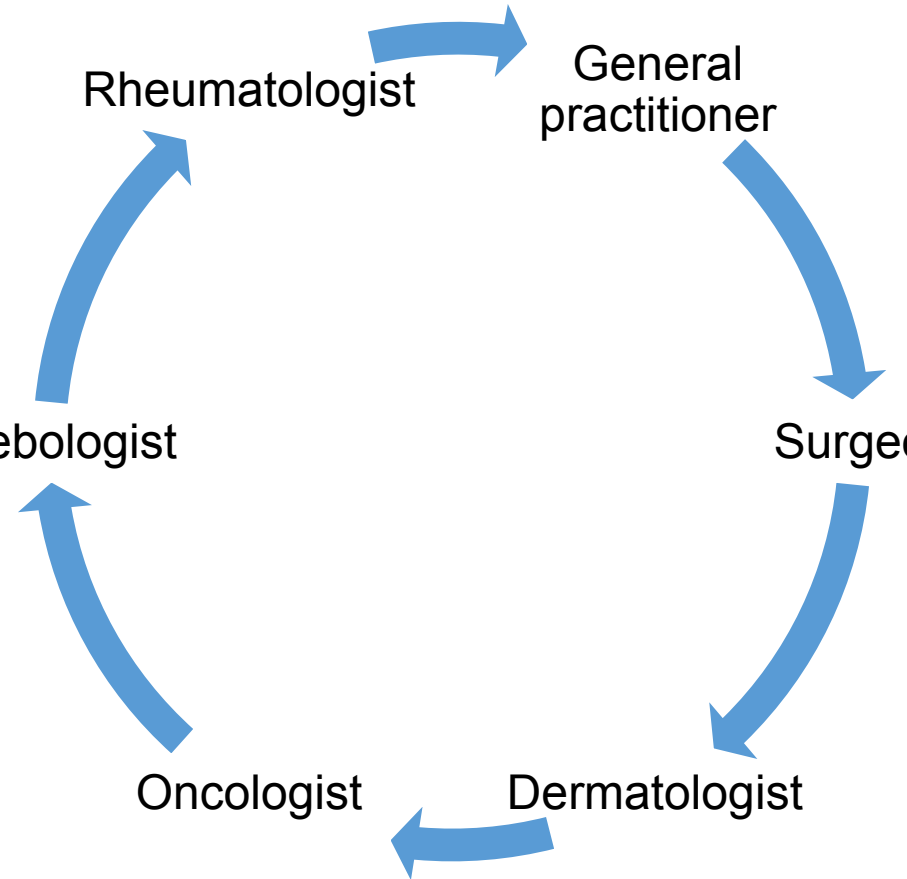
Rheumatologist

General  
practitioner

Surgeon

Oncologist

Dermatologist





# Case Report

42-year-old woman



Osteosynthesis of the left sacroiliac joint and pubic symphysis with nickel-chrome containing reconstruction plates

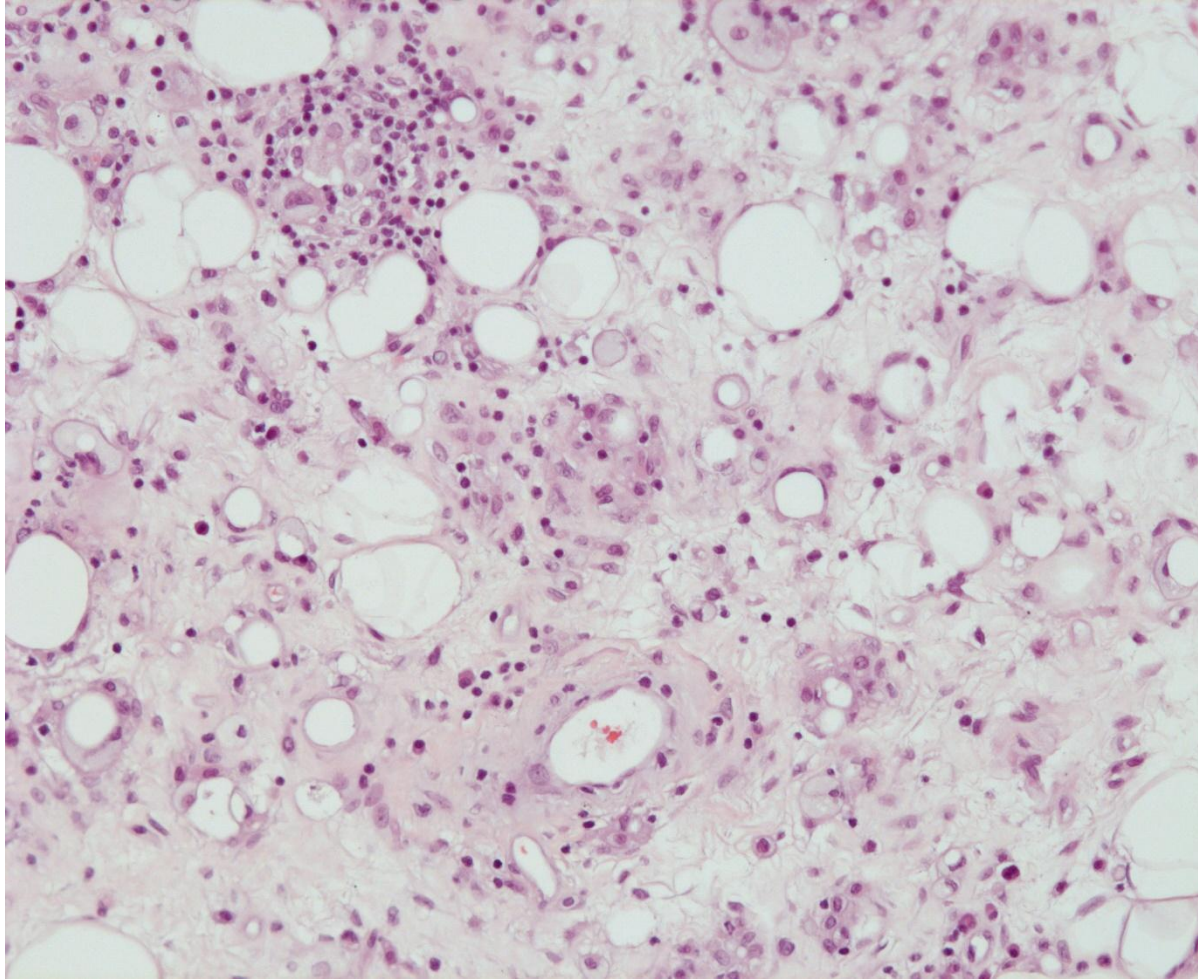


- Fever
- Wound purulent-oily exudate (no pathogenic flora found)
- Painful, self-ulcerated red nodules in the anterior abdominal wall and pubic region
- Fibromyalgia and arthralgia of her hip and knee joints
- Backpains
- Chronic fatigue

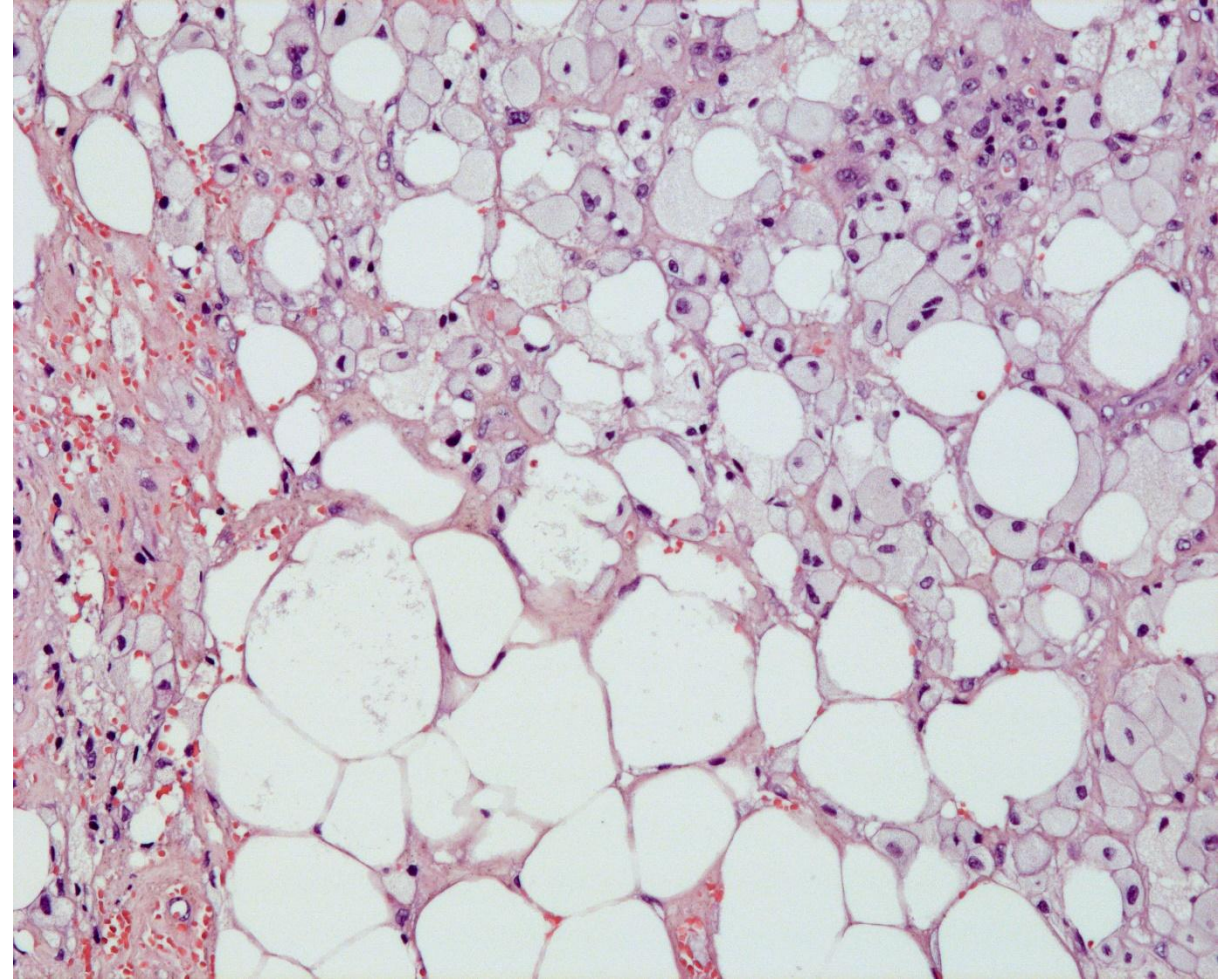




# Histopathology



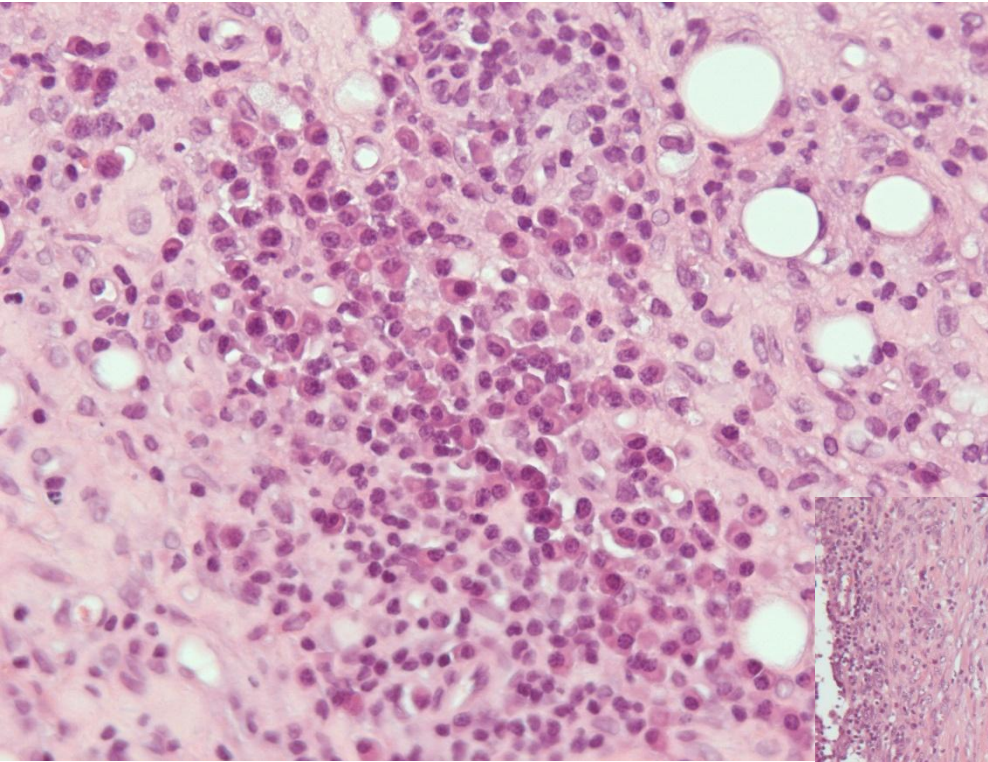
Disruption of adipocytes shows fine vacuolization, diminished size and dropout of adipocytes



Lipid laden macrophages (lipophages) due to phagocytosis of adipocytes, signs of haemorrhages

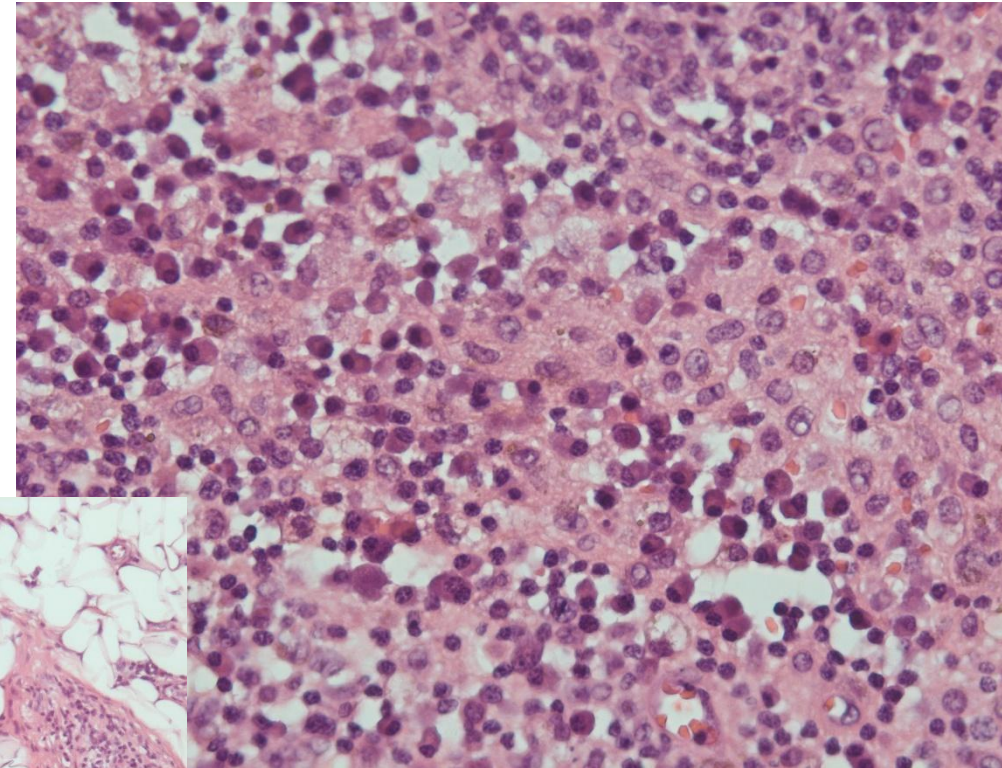


# Histopathology

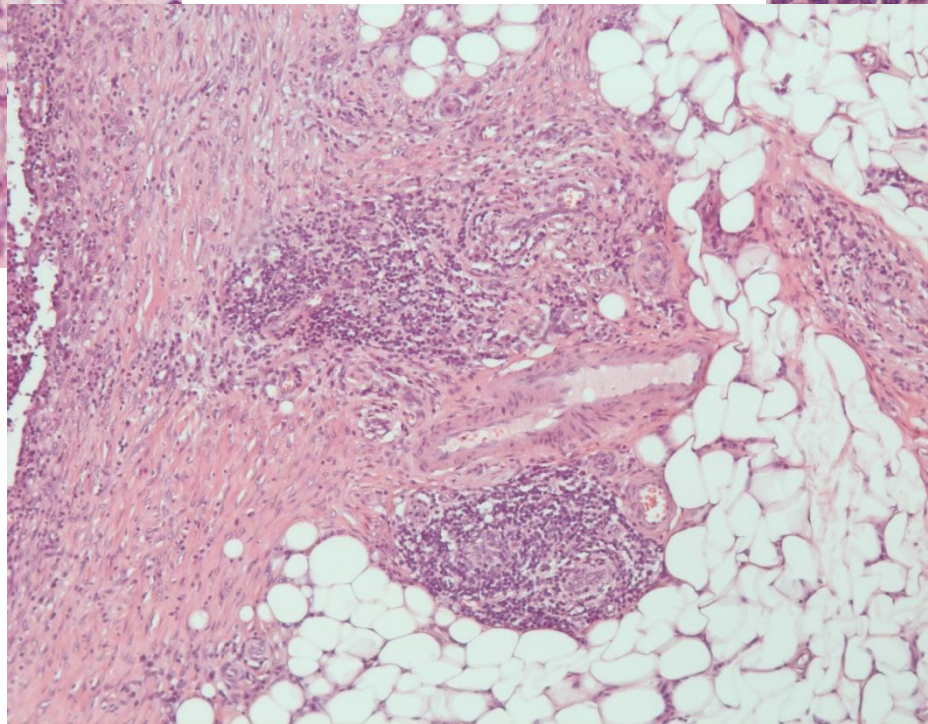


↑  
Necrotic adipocytes surrounded by mixed inflammatory infiltrate of lymphocytes, plasma cells, histiocytes and eosinophils

Lipid laden histiocytes, lymphocytes, plasma cells and focal hemorrhage.



←  
Lymphohistiocytic inflammation of the adipose lobules with foci of liposclerosis and liponecrosis, nodules resembling histiocytic granulomas were formed



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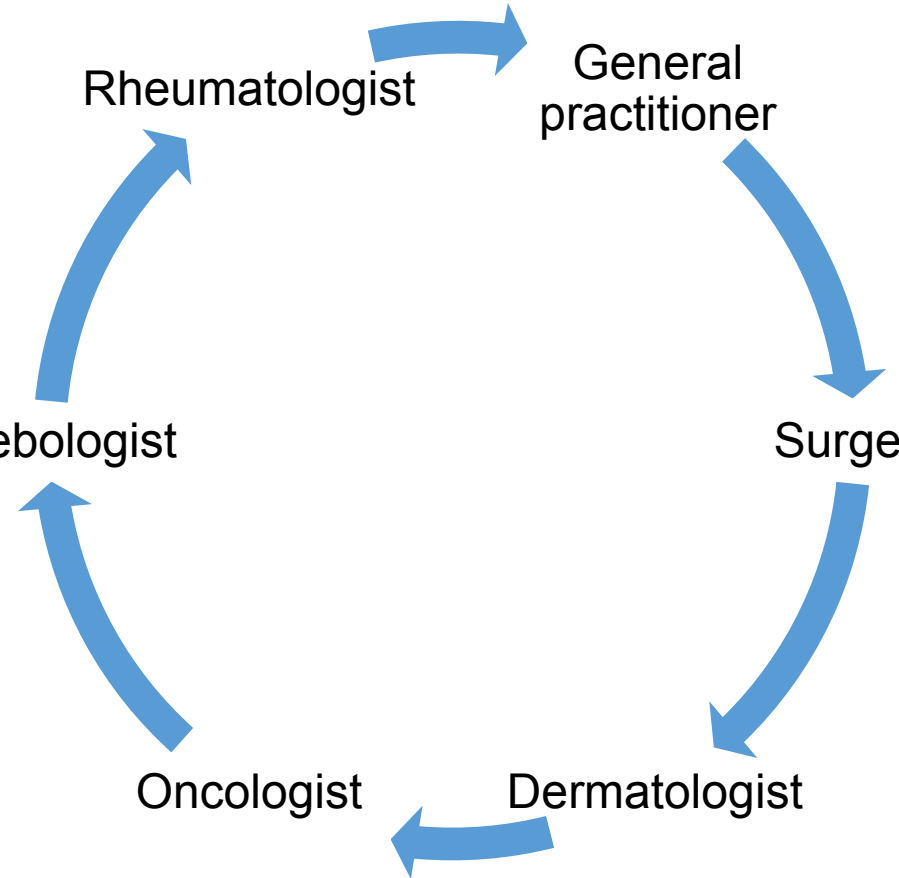
Rheumatologist

General  
practitioner

Surgeon

Oncologist

Dermatologist





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