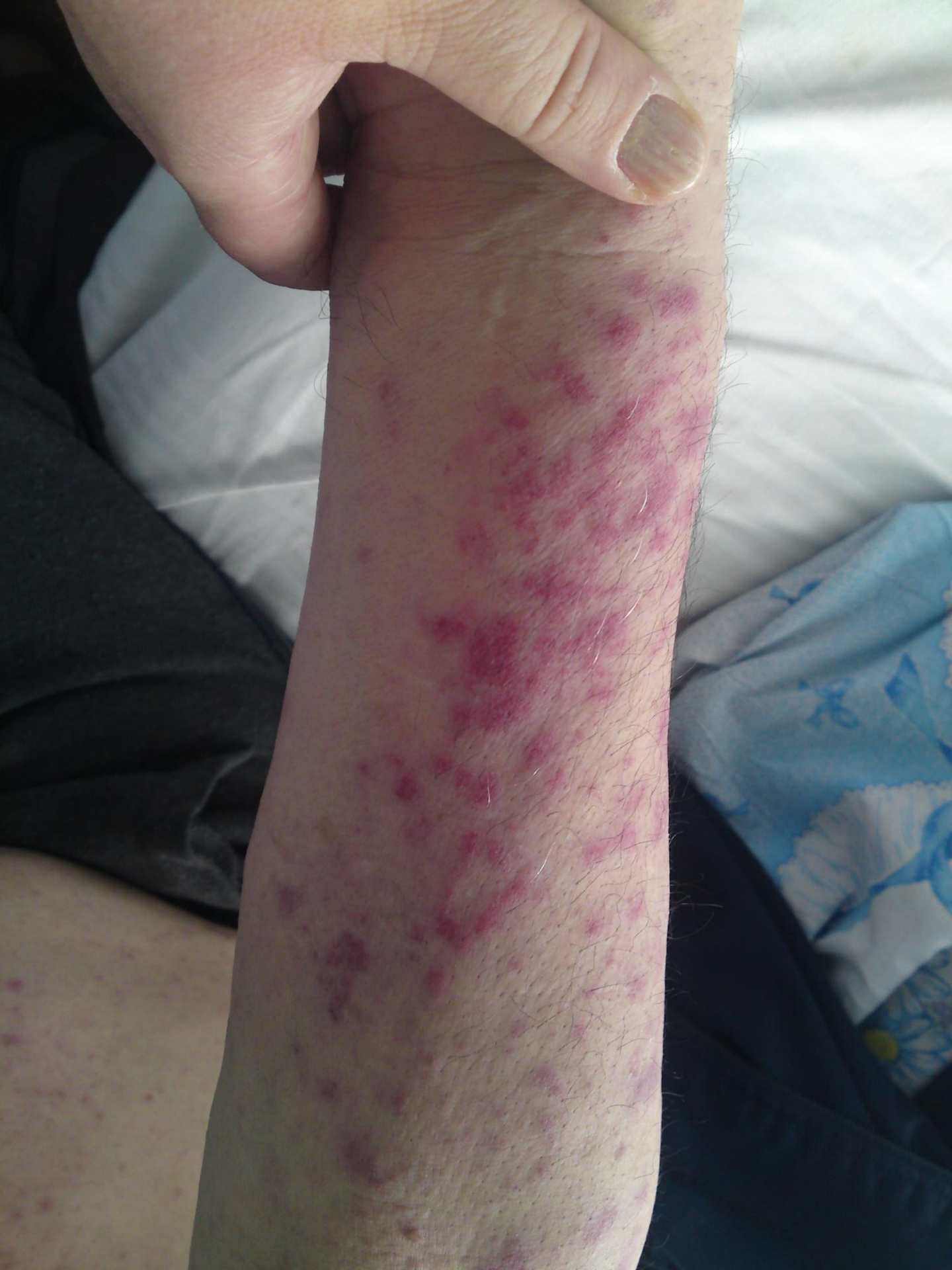
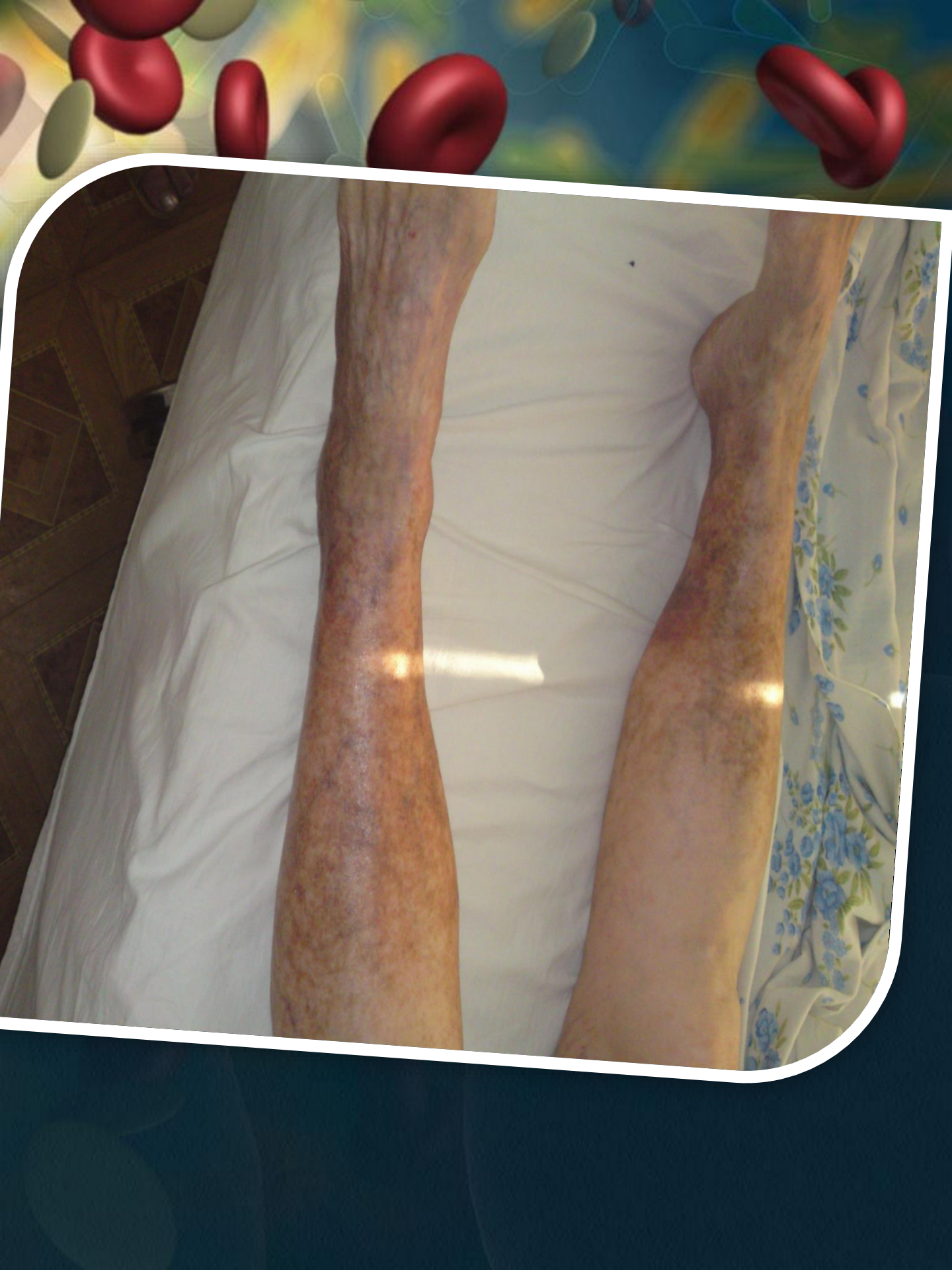
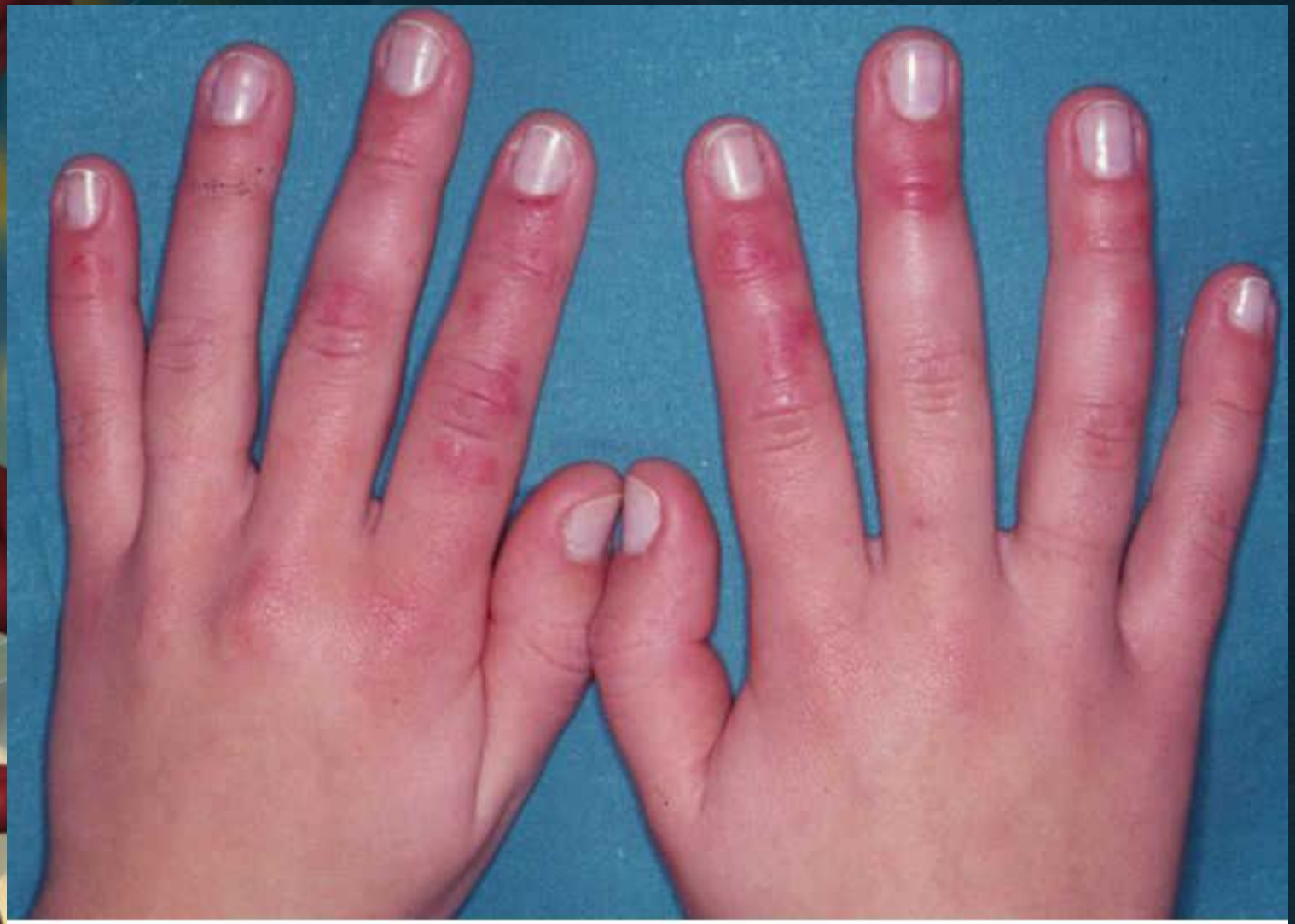
Differential diagnosis of vasculitis







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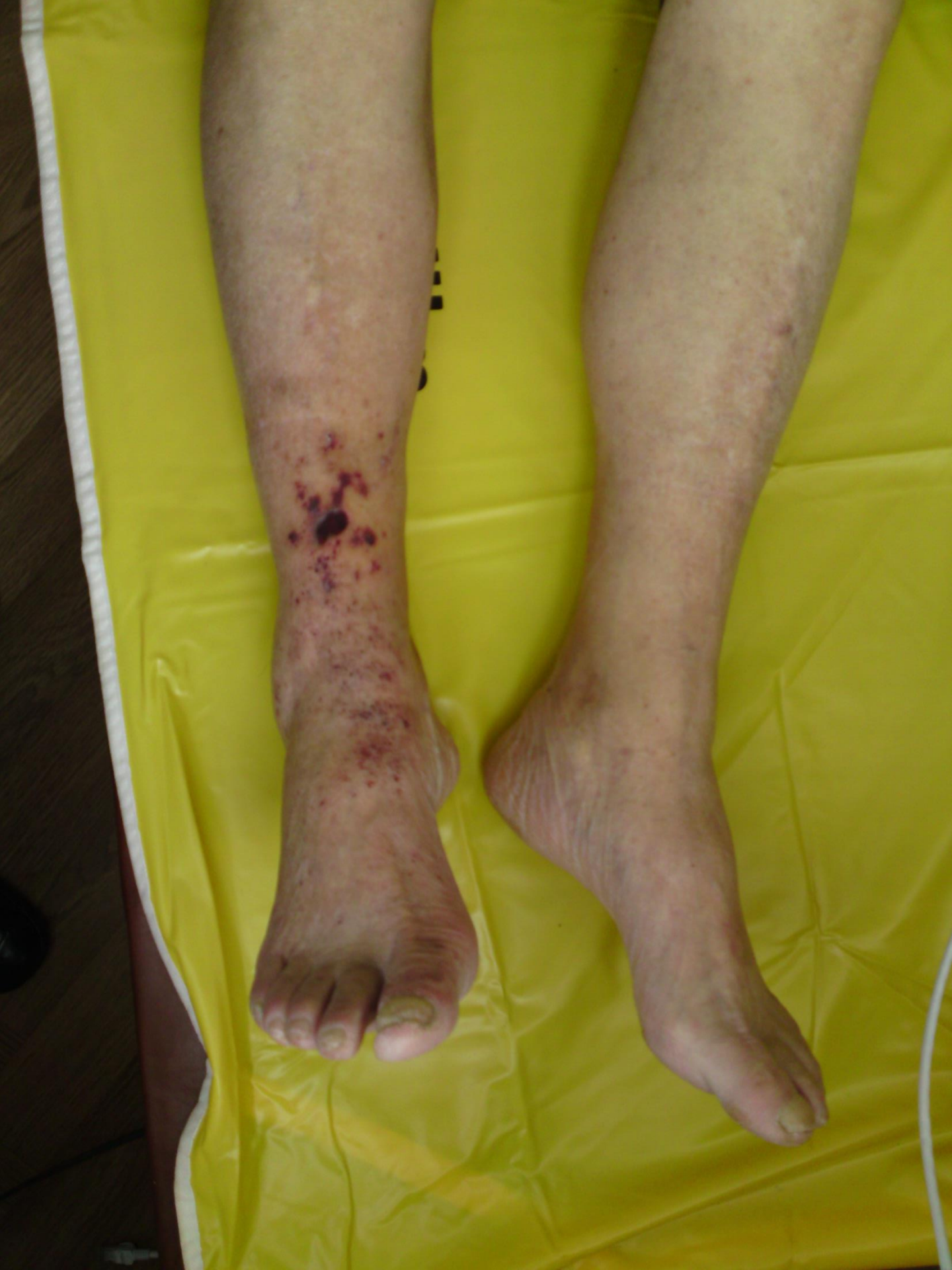
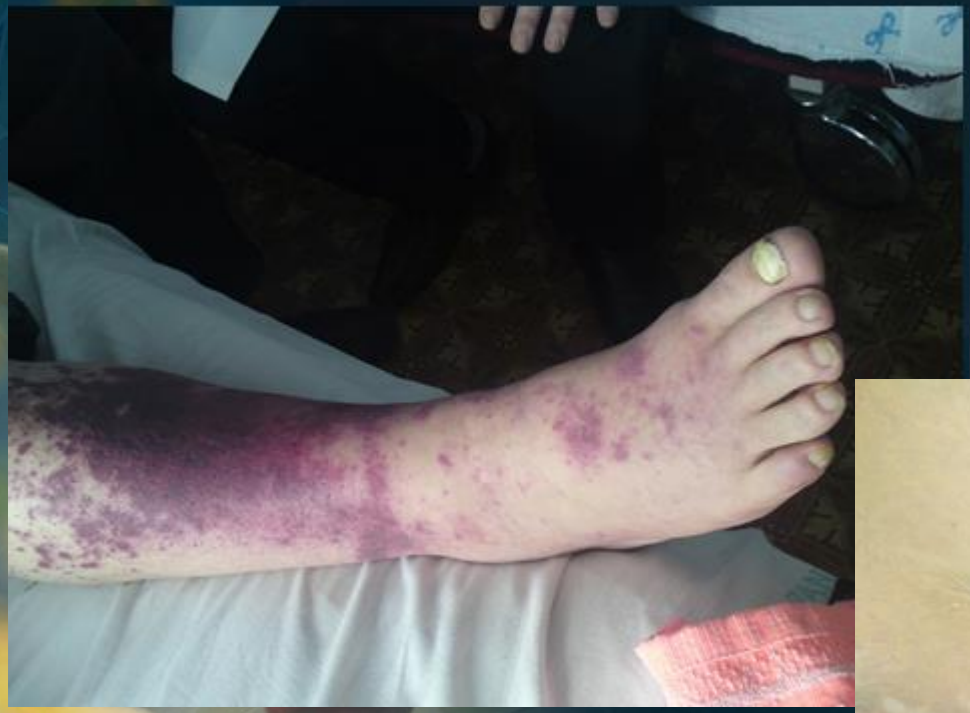
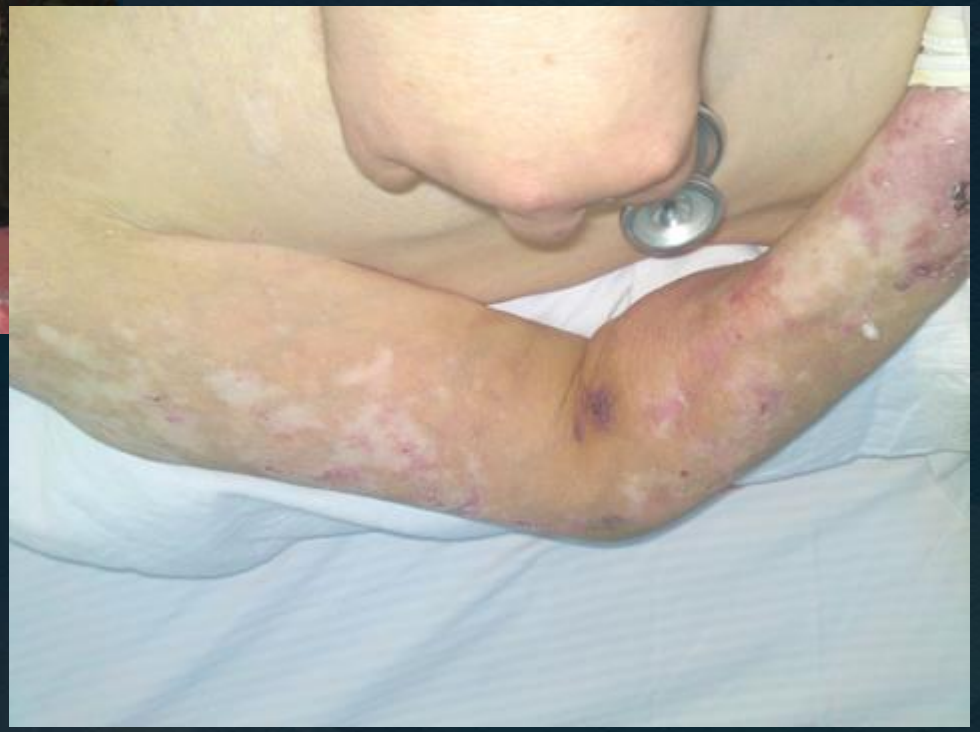
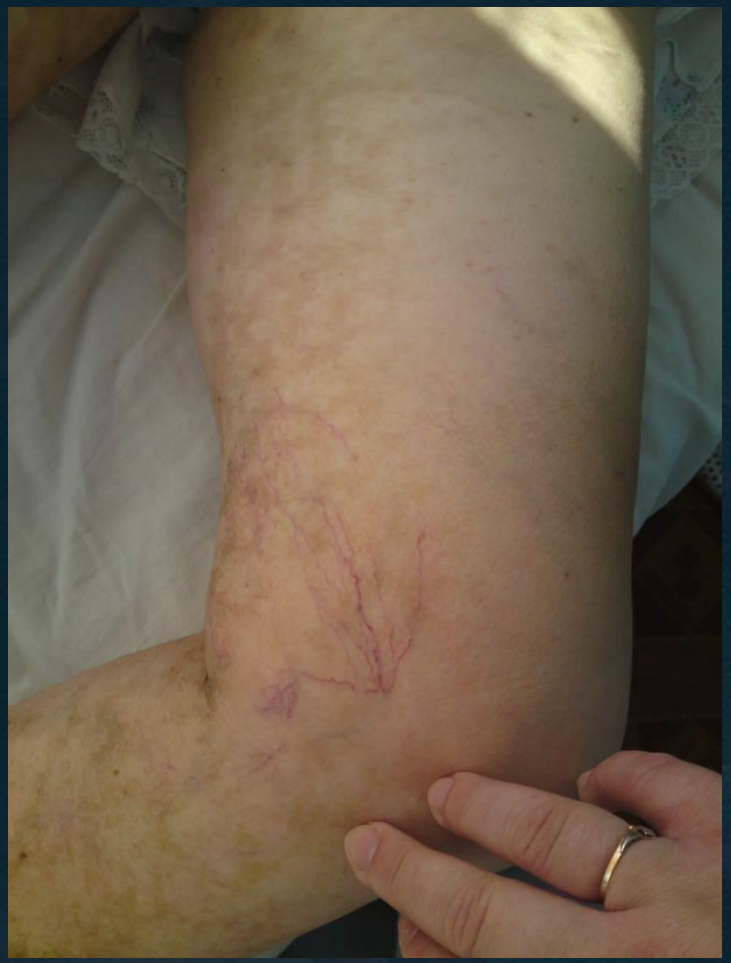
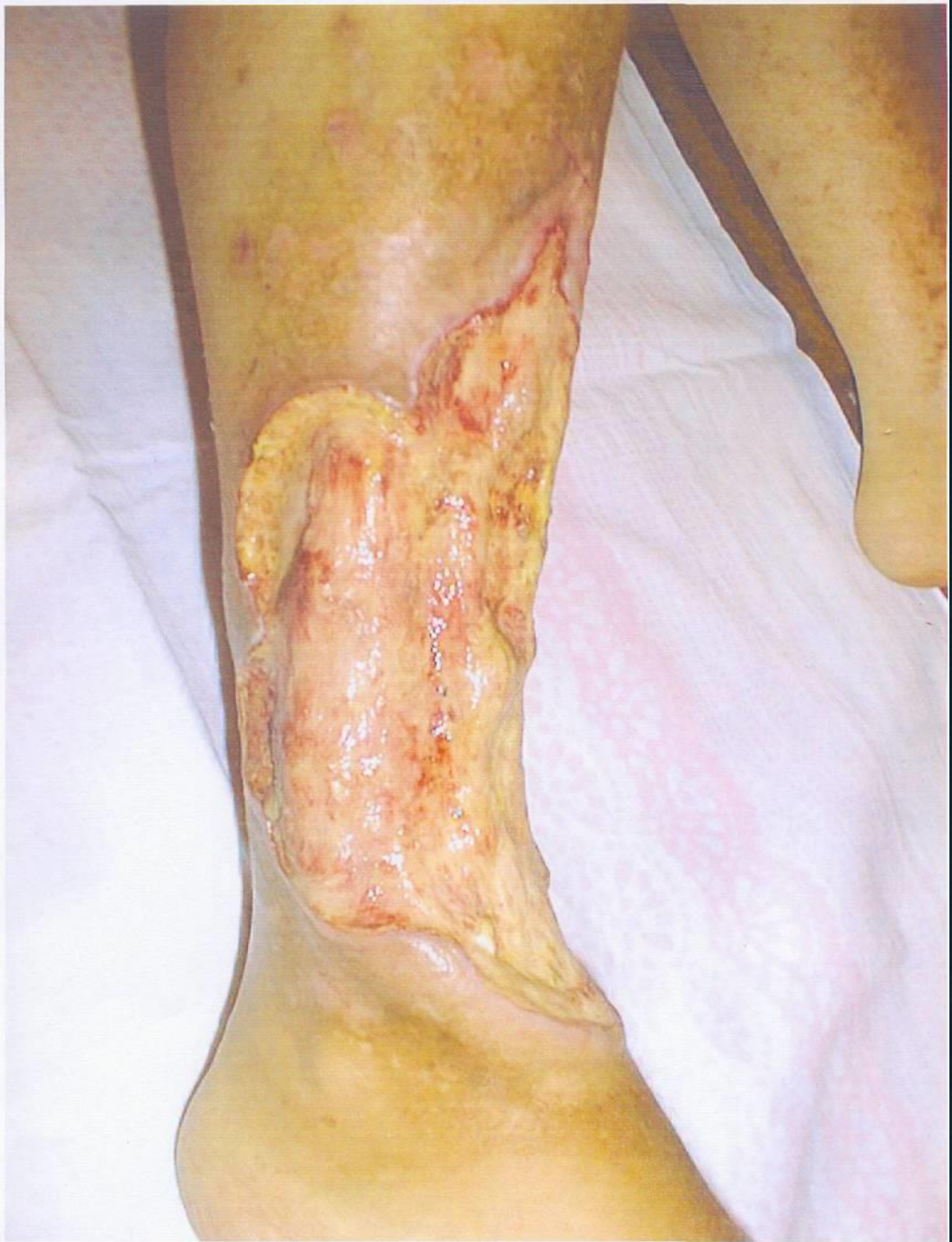
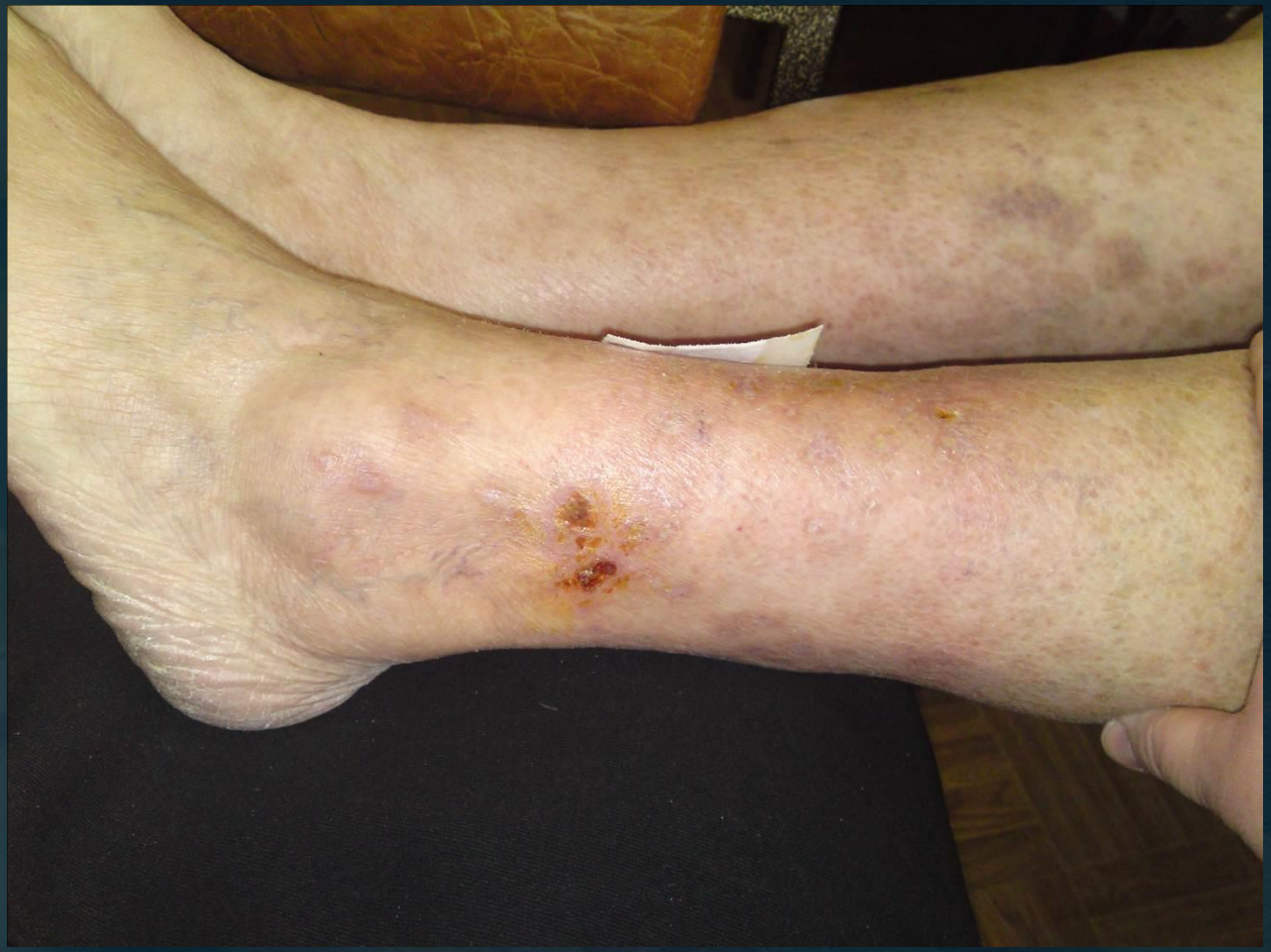








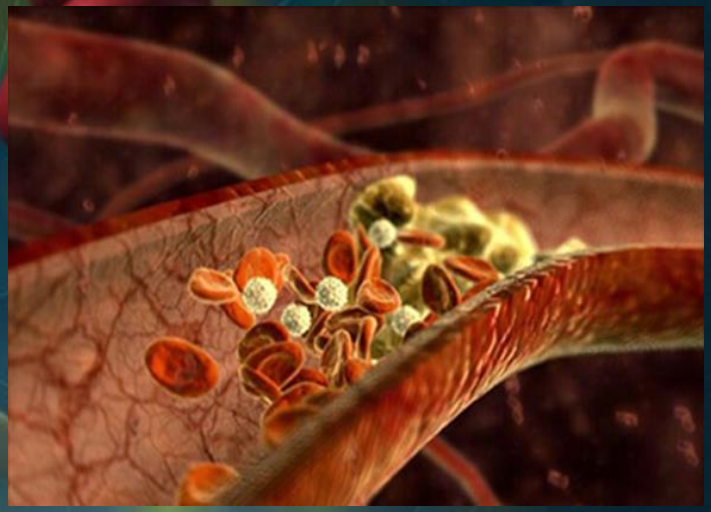




Definition

- **The vasculitis are a heterogeneous group of diseases, involving inflammation of blood vessels with subsequent tissue destruction and/or organ failure, linked by common clinical, laboratory, and pathophysiologic features.**

(Chapel Hill Consensum 2012)



The inflammatory process in the vascular wall may be:

1. Idiopathic (systemic vasculitis (SV)) or

2. Secondary, developing in other diseases (systemic diseases of the connective tissue, tumors, infections, etc.)

The spectrum of vasculitis is varied and includes several nosological entities, individualized by their clinical features, by primarily affected organs and systems, as well as by the changes in laboratory and instrumental investigations.

- **<u>The clinical expression of V. are determined by:</u>**
- ***General signs* and symptoms of inflammation**

and

- ***Tissue ischemia* as a result of narrowing or occlusion of the vessel lumen**
- **Vascular inflammation may be the seat of a cellular infiltrate and fibrinoid necrosis (granulomatous vasculitis).**

Vasculitis = Inflammation of the Blood Vessel

Blood vessel damage

Thickening of vessel wall

Luminal narrowing
or occlusion

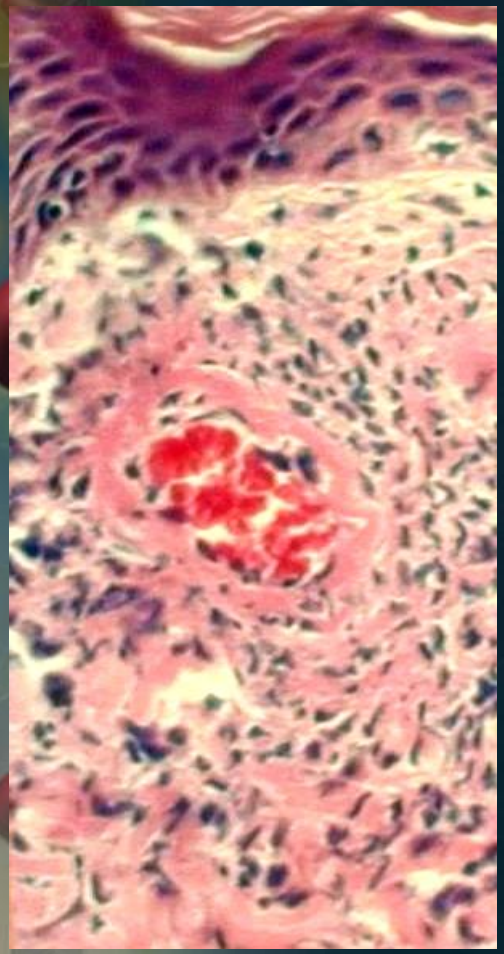
Tissue or organ ischemia

Attenuation of vessel wall

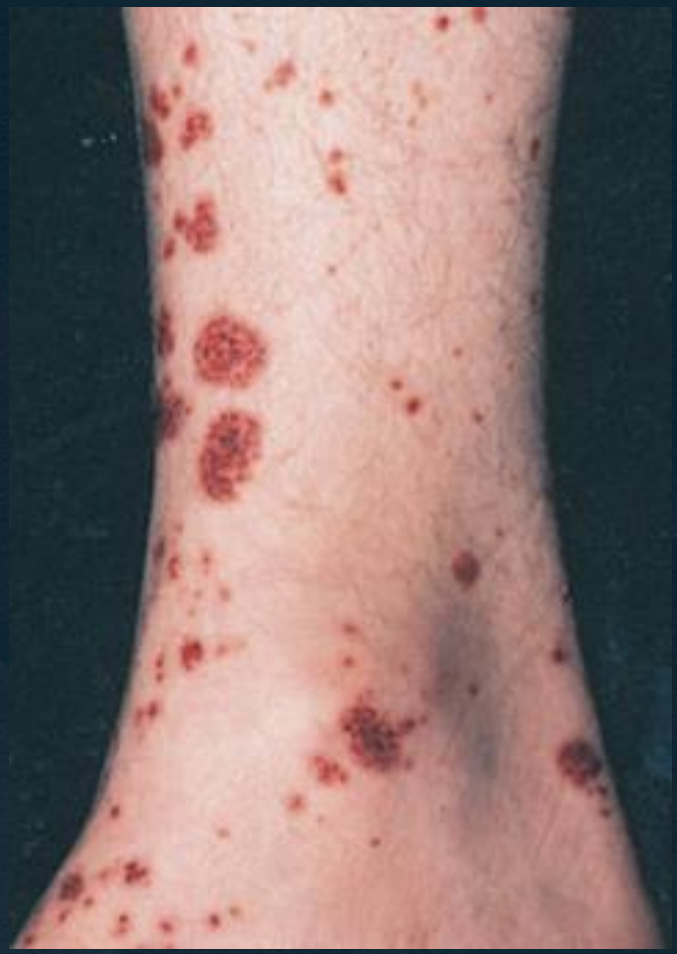
Vessel wall thinning

Aneurysm formation or
Disruption of the vessel wall
with hemorrhage into tissue

Vasculitis: Histological and Clinical Correlation



Disruption of the vessel wall with red blood cell extravasation into tissue



Palpable Purpura

Epidemiology

- ***Certain tendency - increase the incidence of systemic vasculitis among the general population:***

  - improving the diagnostic possibilities

  - **natural increasing**

  - **increased patient survival rate due to newer treatments** ***(the incidence rate for example of ACG (Horton) is 10.9% per year [Petursdottir et al.] .***

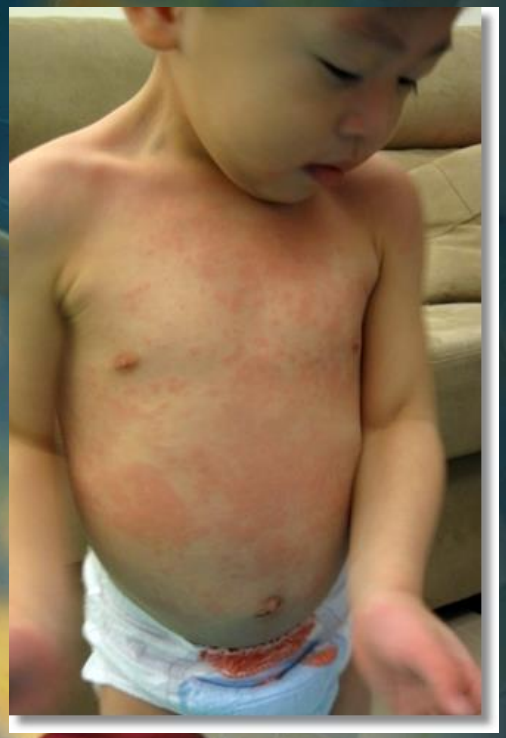
The results of investigations in Sweden, the United Kingdom, Norway - an increase of up to 4 times the incidence of GPA over a period from 1975 to 2005.

The incidence of systemic vasculitis ranges approximately from 0.4 to 14 cases per 100,000 population.

NPA - 0.1–1.6 cases per 1mln populație [Elefante E., Bond M., Monti S. 2018].

Differences in age, gender, ethnicity and geographical spread

Kawasaki **----AGE-------** **GCA (Horton)**



- Takayasu

Behcet

Differences in ethnicity and geographical spread

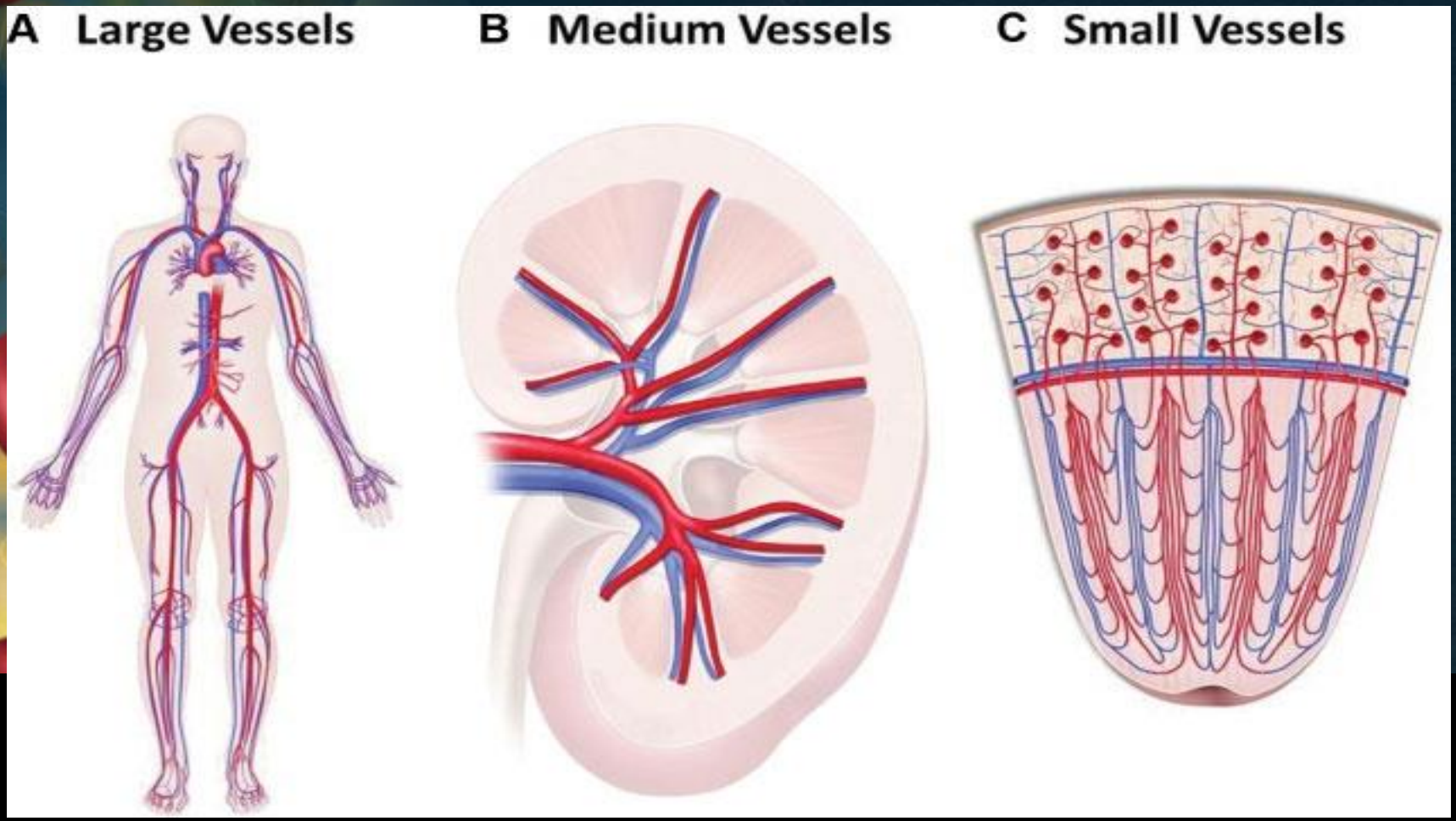
- Granulomatosis with polyangiitis (Wegener's) (GPA)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) , are about 2 times more common in people from Europe.
- The GPA, according to a formal quantification, indicates an increase in incidence up to 3% with each degree of latitude towards the poles.

Giant cell artery disease (ACG): in northern European countries, especially Scandinavia, it is 2 to 3 times higher than in the population of Spain.

Influence of the endemic pattern of infections: for example - cryoglobulinemic vasculitis and polyarthritis nodosa have a close correlation with HCV and HBV hepatotropic infections.

The incidence of some systemic vasculitis

GCA (Horton)	6.7/100 000 - 28.5/100 000 in the elderly >50 y. in Northern Europe [Salvarani et al. 2004]. 10 / 100 000 Southern Europe [González et al. 2001].
Takayasu	0.4 - 0.8 /1mln. (age <40 years) - Denmark [Dreyer et al. 2011], UK [Watts et al. 2009]. 1–2.0 / 1mln. Japan [Koide 1992].
Kawasaki disease	in Japan annually 100 -218,6 / 100,000 children under 5 years old . [Nakamura et al. 2010], (more than 10 times than in Europe and America).
PAN	0.4–2.0 /1 000 000 [Reinhold-Keller et al. 2005].
GPA (Wegener)	8,6 - 11.3/1mln. SUA, UK [Zeft et al. 2005,Watts et al. 2012].
MPA	5.9 la 1 000 000 population in Europe [Watts et al. 2012]. 18.2 la 1 000 000 Japan [Fujimoto et al. 2011].
EGPA (Churg – Strauss)	1.2 -2.3/1 000 000 [Ormerod et al. 2008, Vinit et al. 2009].
IgA vasculitis (Henoch–Schöenlein purpura)	At Children: 10.2 – 20,4/100 000 – in Europe [Dolezalova et al. 2004, Gardner-Medwin et al. 2002]. 3.5/100 000 Japan [Kawasaki et al. 2010]; At maturity: 3 – 13/100 000 [Watts et al. 1998, Dadoniene et al. 2005].


A Large Vessels
B Medium Vessels
C Small Vessels

2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

1. Large vessel vasculitis

1.1. Takayasu Arteritis

1.2. Giant Cell Arteritis

2. Medium vessel vasculitis

2.1. Polyarteritis nodosa

2.2. Kawasaki disease

3. Small vessel vasculitis

3.1. ANCA – associated vasculitis

3.1.1. Microscopic polyangiitis

3.1.2. Granulomatosis with Polyangiitis (Wegener Granulomatosis)

3.1.3. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

3.2. Immune Complex-Mediated Vasculitis

3.2.1. Anti–glomerular basement membrane (anti-GBM) disease

3.2.2. Cryoglobulinemic vasculitis

3.2.3. IgA-vasculitis (Henoch-Schönlein)

3.2.4.Hypocomplementemic urticarial vasculitis (HUV) (anti-C1qvasculitis)

- **4. Variable vessel vasculitis**
- 4.1. Behçet disease
- 4.2. Cogan's Syndrome
- **5. Single-organ vasculits**
- 5.1. Cutaneous leukocytoclastic angiitis
- 5.2. Cutaneous arteritis
- 5.3. Primary central nervous system vasculitis
- 5.4. Isolated aortiritis
- 5.5. Others
- **6. Vasculitis associated with systemic diseases**
- 6.1. Lupus vasculitis
- 6.2. Rheumatoid vasculitis
- 6.3. Sarcoid vasculitis
- 6.4. Others

Clasificarea CHCC2012 (4)

7. Vasculitis associated with probable etiology

7.1. HCV-associated cryoglobulinemic vasculitis

7.2. HBV- associated vasculitis

7.3. Syphilis-associated aortitis

7.4. Drug-associated immune complex vasculitis.

7.5. Drug-induced ANCA-associated vasculitis

7.6. Cancer--associated vasculitis

Historical Data (1)

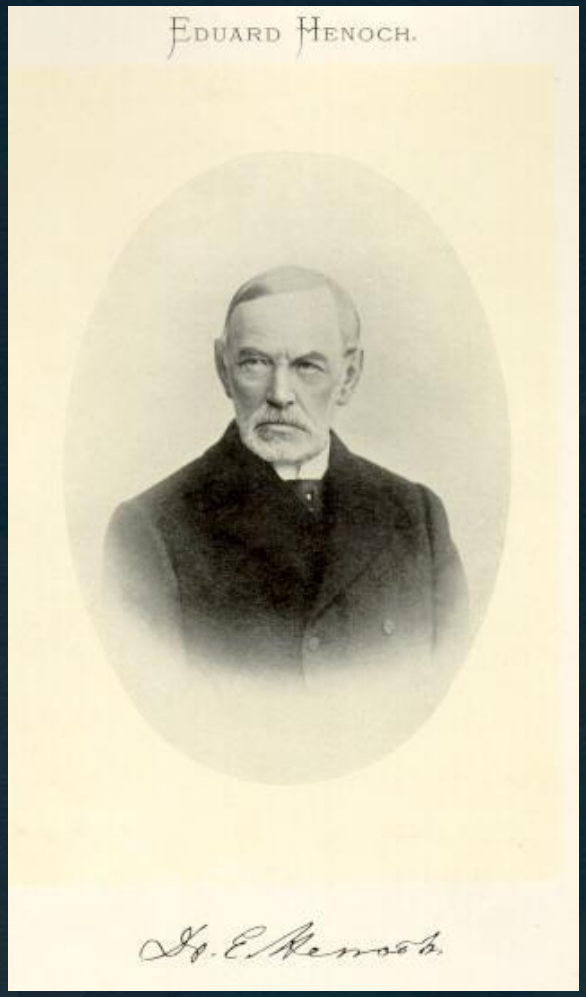
1554 – A.Saporta “luetic aneurysm ”

- Serious and veritable Studies - were more than 150 years ago.
- In 1755 Michaelis and Martani describe the first case of systemic vasculitis.
- În 1866 Kussmaul and Maier reported a clinical case of 27-old years patient with nephritis, abdominal pain, neuritis, which they called polyarteritis nodosa, highlighting and polifocal transmural inflammation.

Istory (2)

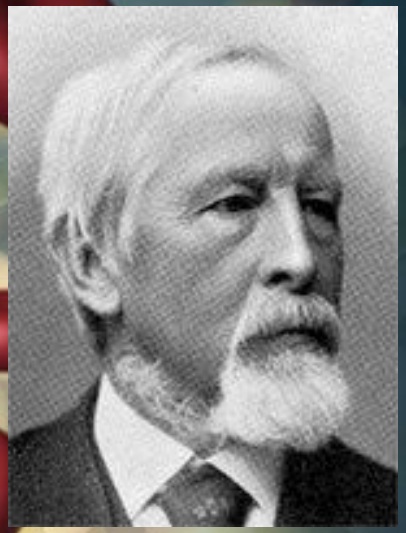
- **In 1837 Schönlein and later - Henoch in 1874, described purpura that bears his name.**

Schonlein

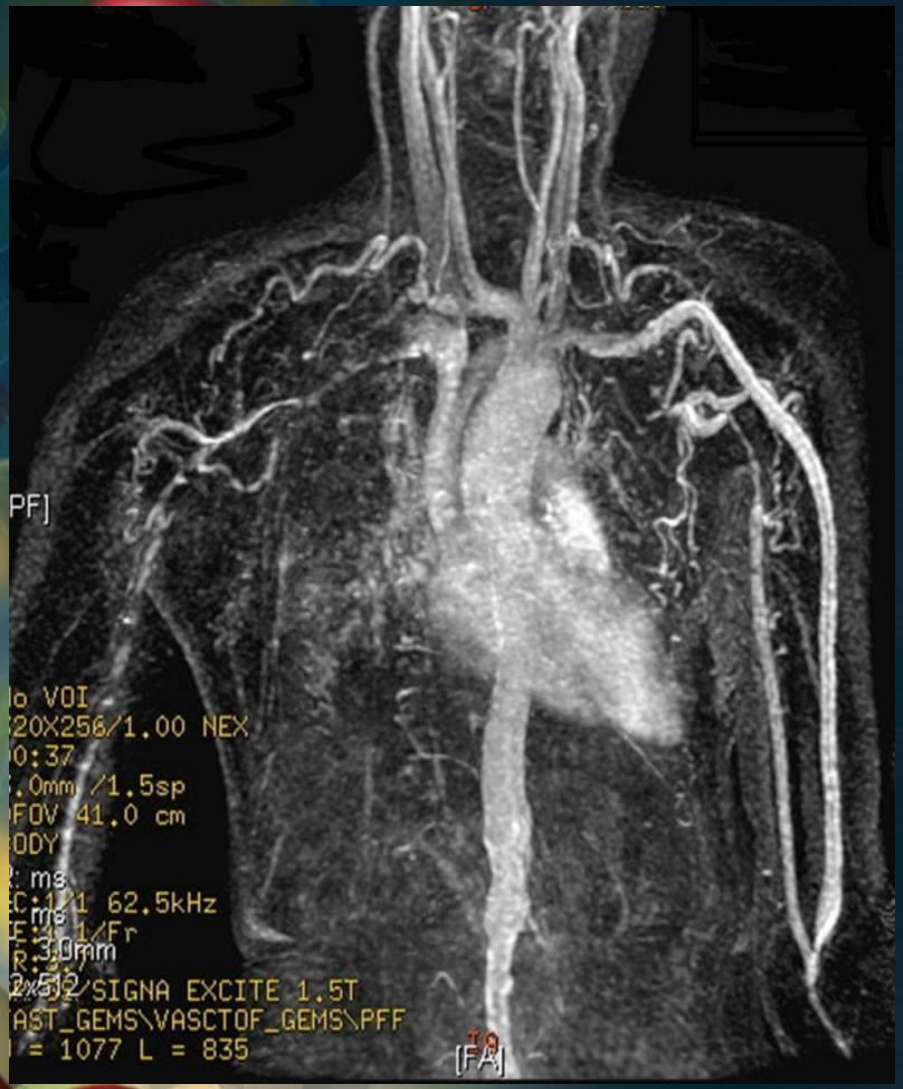


Karel Rokitanskiy

- In 1852 Rokitansky describes the characteristic clinical features of poliarteritis nodosa.
- Extensive research in this disease Kussmaul and Maier's belong in 1966. The great majority of vasculitis have been identified since the twentieth century.



Adolf Kussmaul (1822-1902)



- **1908 – Takayasu describes ischemic changes - result of arteritis that bears his name.**

Mikito Takayasu

- Vasculitis descriptions continues with Wegener's granulomatosis, Behcet's disease, Churg Strauss (1951), the hypersensitivity vasculitis (1984).

Etiology & pathogeny

- VS are very heterogeneous disease, for which reason - not assume a single etiology.
- In most cases the **cause remains unknown**, but eventually it does not substantially influence the evolution of the disease process.

- *There have been proposed etiologies:*
- **I.Infectious theory (dominates).**
- **In several nosologic versions of SV is determinated a definite immunological link with various infectious agents.**
- **The presence of chronic infections, even if they were not the direct cause of disease may promote the recurrence of VS and the development of complications.**

- Although resistant to the penetration of infections, vascular wall becomes vulnerable in some situations:
- Infection from adjacent tissues (the tissue surrounding)
- or inside - blood

  - toxic or immunologically induced infection of endothelial cells and other vascular structure

- It is assumed that virtually any infectious agents (HAV, HBV, HCV, Cytomegalovirus, HIV, Epstein –Bar, Parvovirus B19, streptococci, stafilococci, borellia, klebsiella, hlamidia, yersinia, salmonella, micobacteriae), are able to cause inflammatory reactions in different size vessels.
-

- **Are incriminated viruses, which can contribute to vascular inflammation, either directly by altering endothelial cell and disruption of its functions or indirectly, by participating in the formation of immune complexes.**
-

II. The role of drugs

- The role of drugs is found (established) in many situations as a potential cause of some nosologic versions of VS
- Sulfonamides, antibiotics, contrast agents, preparations containing iodine, tuberculostatics, preparations, gold drugs and al.)
-

III. Genetic predisposition

- Genetically compromised background
- Defective immune response and altered reactivity of the vascular wall.
- Association of HLA phenotypes with certain vasculitis

Vasculitis	HLA - association
Takayasu arteritis	**HLA B5 (B52 in Asia)**
Granulomatosis with polyangiitis (Wegener's) (GPA)	Protective effect of DR 13
Kawasaki Disease	B51 in Caucasian, B22 - Japanese
Giant cell arteritis (GCA)	HLA-DR4
Behcet disease	HLA-B51
IgA vasculitis (Henoch-Schoenlein) (IgAV)	Abnormalities of complement genes (III class HLA)
Rheumatoid vasculitis	DR4 (DRB 1 *04)

Pathogenesis of systemic vasculitis includes the following events:

- **Damage to the vascular wall**
- **Ischemic disorders in the tissue surrounding the affected vessel**
- **Granuloma formation.**

. Immune mechanisms

- **The mechanism of histological lesions in SV is immunological one, by immune complexes, or more rarely, through the mechanism of cell-mediated hypersensitivity.**
- **In some situations it is possible the association of both mechanisms.**

- ***Evidence of mechanism by immune complex in vasculitis are:***
- **association with serologic abnormalities (the presence of CIC, cryoglobulinemia, reumatoid factor, hipergamaglobulinemia, hipocomplementemia),**
- **detection by immunofluorescence of IgG and complement in concerned vessels,**
- **occurrence of vasculitis in some diseases, produced by immune complex pathogenic mechanism (SLE).**

- **Antigen in immune complexes is rarely identified. It can be both endogenous (IgG) as well as exogenous. In some vasculitis was found hepatitis B antigen.**

- **Pathogenetic mechanisms suspected to cause vascular injury include:**
  - Formation of pathogenic circulating immune complexes **and**
- **storing them in the vessel wall that causes inflammation**

- - autoantibody formation, such as: anti-endothelial cell antibody, ANCA and/or neutrophils mediate lesion of endothelial cell.
-

- damage to endothelial cells mediated by T lymphocytes
- Molecular and cellular immune response, including the secretion of cytokines and adhesives molecules.

- Direct infection of endothelial cells, their direct damage by the micro-organisms, tumor cells, toxins
- - formation of granulomas

ESSENTIAL PATHOGENETIC COMPONENTS

- CIC
- Circulating immune complexes ANTIGEN+Antibody

- CIC - have greater importance in vasculitis caused by infections and drugs.

- **Immunoglobulins + complement components (ex. leucocitoclastic vasculitis, CIC containing IgA in hemorrhagic vasculitis; Cryoglobulinemia – immune complexes precipitated from cold, polyarteritis nodosa, associated with HBV infection, s. Churg – Srauss, organospecific autoantibody in Kawasaki disease.**

Anti-endothelial cell antibodies (AECA)

- Determined by enzyme immunoassay
- AECA – A heterogeneous group of autoantibodies which react with the vascular endothelium of fragment F (ab ').
- Possess the ability to bind complement and exhibit cross-reactivity with other cells (- ie. Fibroblasts).
- In some forms of vasculitis AECA may injure endothelial cells by complement-dependent cytolisis.
-

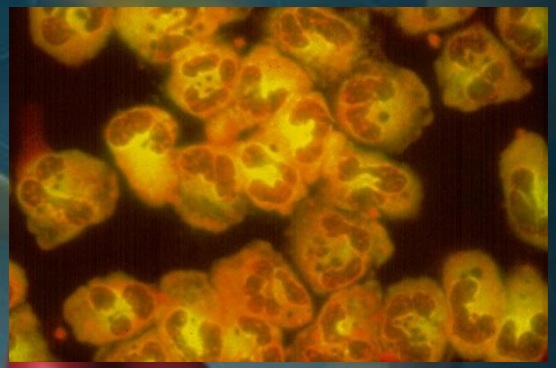
ANCA – Anti-neutrophil cytoplasmic antibodies (ANCAs)

- the presence of autoantibodies against cytoplasmic constituents of neutrophils

  and monocytes, designated as ANCAs are a group of autoantibodies, mainly of the IgG type, against antigens in the cytoplasm of neutrophil granulocytes (the most common type of white blood cell) and monocytes. They are detected as a blood test in a number of autoimmune disorders, but are particularly associated with systemic vasculitis, so called ANCA-associated vasculitides.

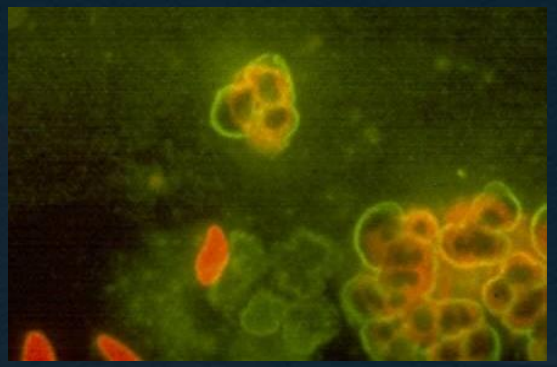
Antineutrophil Cytoplasmic Antibodies (ANCA)

cANCA
cytoplasmic staining



Courtesy of Carol A. Langford

pANCA
perinuclear staining



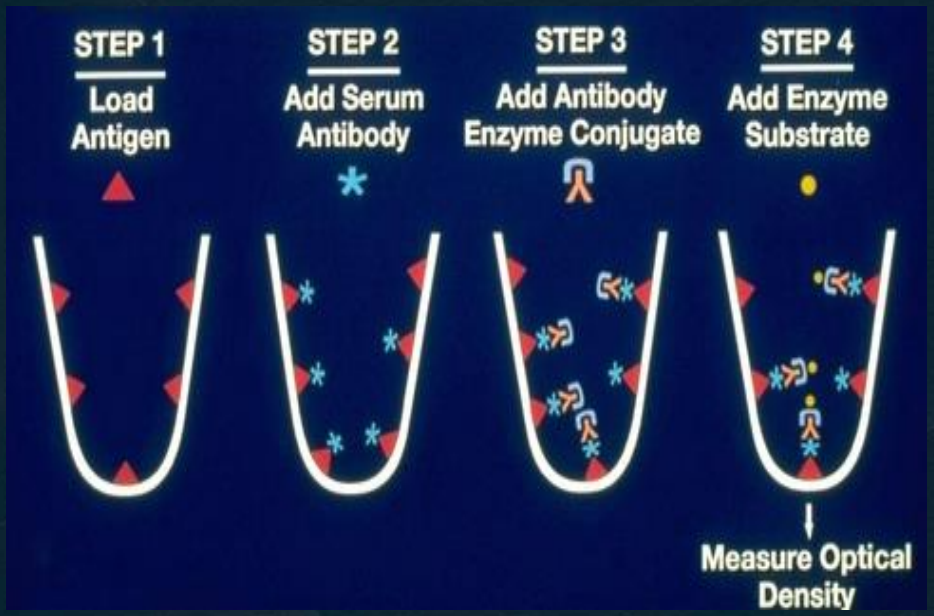
Courtesy of Carol A. Langford

Target Antigens In Vasculitis

	Proteinase 3 (PR3)	Myeloperoxidase (MPO)	
	PR3-ANCA	MPO-ANCA	ANCA (-)
Wegener's granulomatosis	75-90%	5-20%	up to 20%
Microscopic polyangiitis	10-50%	50-80%	up to 20%
Churg-Strauss syndrome	3-20%	2-40%	up to 60%

Antineutrophil Cytoplasmic Antibodies

- ANCA by ELISA methods
  - Proteinase 3 (PR3) = Wegener's disease
  - Myeloperoxidase (MPO) = MPA



ANCAs are autoantibodies that attack the inside (cytoplasm) of neutrophils.
When ANCAs attack these neutrophils, they cause the white blood cells to attack the walls of small vessels in different tissues and organs of the body.

Cryoglobulins

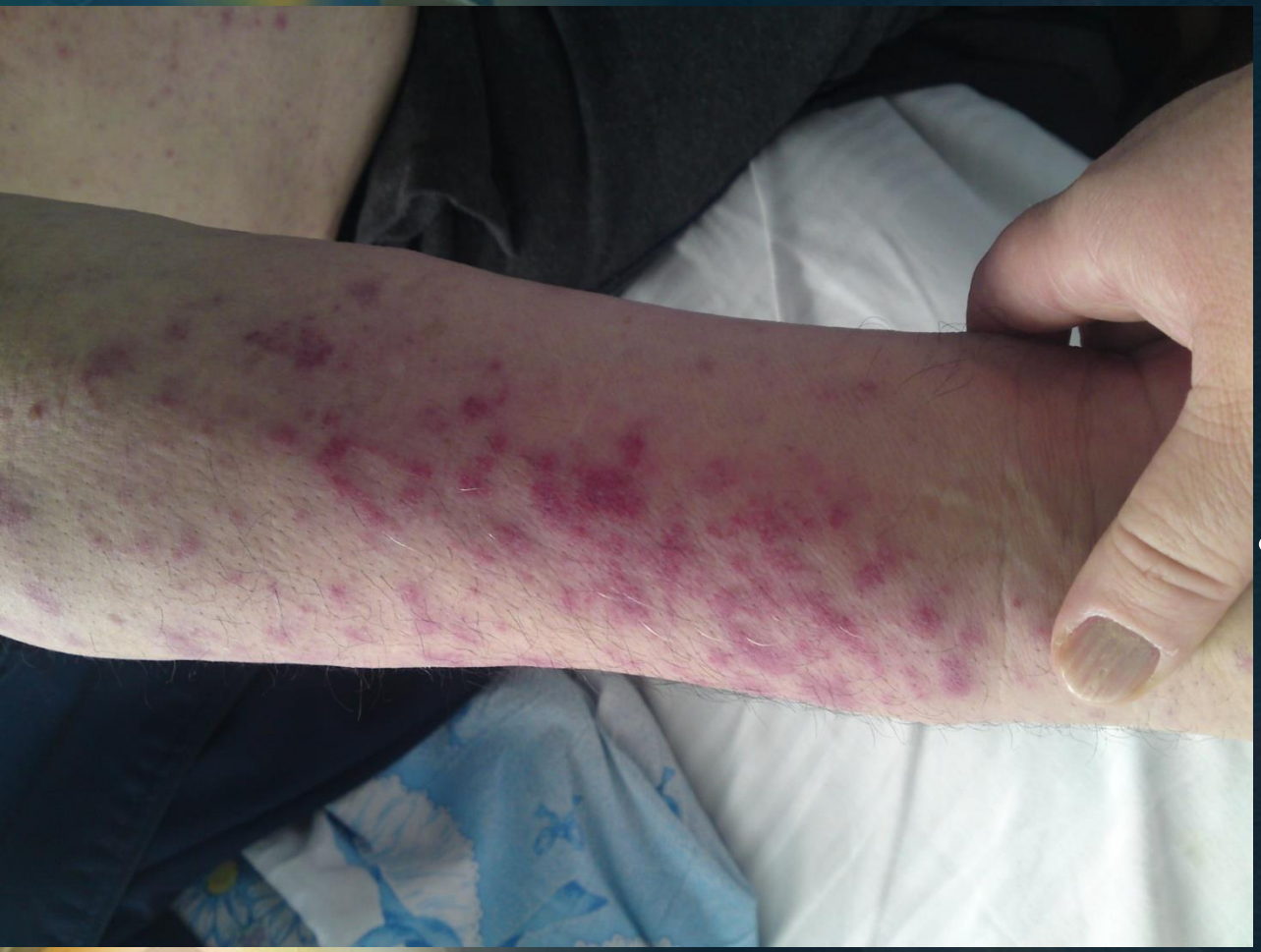
- **Cryoglobulins are cold-precipitable immunoglobulins.Three types of cryoglobulins are detectable:**
- **Type I,** in 10% to 15% of patients, consists of monoclonal IgM-RF and originates in the context of a lymphoproliferative or myelo-proliferative disease.
- **Type II,** occurring in 50% to 60% of patients, consists of monoclonal IgM-RF and polyclonal IgG.
- **Type III**, found in 30% to 40% of patients, consists of polyclonal IgM-RF and polyclonal IgG.

Clinical presentation

The most common constitutional symptoms are:

- **fatigue,**
- **general weakness,**
- **fever and**
- **arthralgia.**

Some clinical signs suggesting the presence of vasculitis:



- **Purpura or other type of rashes (eruptions)**

Skin lesions that do not disappear under digital pressure due to intracutaneous bleeding.

Mononeuritic multiplex

- **Occurred when there are injured two or more nerves in separate parts of the body.**

- **Pulmonary involvement**
- Alveolar hemorrhage from the capillaries can cause hemoptysis. Hemoptysis can also occurs in medium vasculitis (rupture of an aneurysm of the bronchial arteries).
- **Renal involvment**
- Membranoprolipherative glomerulonephritis, nephritic or nefrotic syndrome.

Clinical signs in vasculitis	
Large vessels	**Pulse deficit**
	Murmurs
Medium vessels	**Cutaneus nodules**
	Livedo reticularis
	Digital infarctions
Small vessels	**Palpable purpura**
	Superficial ulcerations
	Mononeuritic multiplex
	Papulonecrotic injury

Laboratory tests

Very important in elaboration of positive and differential diagnosis, assessment of vasculitis activity, effectiveness of treatment.

- **Blood count may reveal:**
- **anemia,**
- **thrombocytopenia,**
- **leukocytosis,**
- **ESR elevation,**
- **eosinophilia (Churg-Strauss**).

- **Urinalysis and other urine tests, kidney function tests**– assessment of any kidney damage.
- **Biochemical analysis of blood: creatinine, urea** (renal involvement) ;
- **hepatic enzymes** (vasculitis secondary to viral hepatitis; treatment side effects VS);

- **Exams which will investigate the presence of possible infection:** Viral hepatitis markers (HBV, HCV, HDV), ASL-O, MRS, HIV et al.
- **Bacteriological examination:** faringeal (throat swab), blood (in fever), urine culture.

Immunological tests are the most important:

- **Determination of ANCA**
- **Cryoglobulins**
- **Immunoglobulins (especially IgA)**
- **Antinuclear antibodies, antiADNds, Rheumatoid factor, anti-CCP (for the differential diagnosis)**
- **endothelial antibodies**
- **Complement.**

Instrumental methods

- X- Ray Diagnosis of pulmonary damage (Granulomatosis with polyangiitis (Wegener's) Vasculitis, Microscopic
- Polyangiitis (MPA), and Churg-Strauss syndrome).
- Angiography - in the diagnosis of Takayasu arteritis , Polyarteritis nodosa (PAN).

Ultrsonografic examination of the heart and vessels:

in Kawasaki disease, Behcet disease, PAN, Takayasu arteritis, obliterant trombangiitis –

- to confirm the diagnosis,
- assessment of inflammatory process extension in the vascular bed.

TC, RMN, RMN-angiography

- - to assess the topography of vascular lesions (**Giant cell arteritis**, Churg-Strauss syndrome, Takayasu arteritis, **Granulomatosis with polyangiitis (Wegener's) Vasculitis** and al.)

- . **Bronchoscopy and bronchoalveolar lavage - Churg-Strauss syndrome.)**

- **Morphological examination: it is essential for the diagnosis of Granulomatosis with polyangiitis (Wegener's) Vasculitis, Microscopic**
- **Polyangiitis (MPA), and Churg-Strauss syndrome.**
- **The s**amples are usually collected from: skin, temporal a., muscles, respiratory system, lungs, rarely - bowel, liver. However, especialy in the onset of diseases, specific morphological signs may be absent.

Treatament - Objectives (aims):

- Cessation of active process and remission achieving
- Maintaining remission and preventing new flare
- Preventing complications, irreversible damage of tissues and organs irrigated by affected vessels.
- Avoiding side effects of treatment
- Improving quality of life and diseases
- prognosis .

Etiological treatment

- – Treatment with the highest efficiency.
- It is particularly important in those variants that are clearly connected with infection. (PAN, cryoglobulinemic vasculitis, Immunoglobulins IgA vasculitis-S-Henogh)
- Antibiotics
- Interferonotherapy
- Ig I/V

Pathogenetic treatment

- In case of lack of knowledge about the etiology
- Aggressive, immunosuppressive treatment - which is determined by the activity of inflammation and destructive process in the vascular wall.

The treatment includes three phases:

- induction of remission,
- maintenance, and
- treatment of relapse.

The severity and extent of the disease divides patients into three groups:

- ✓ those with localized or early disease,
- ✓ those with generalized disease with threatened organ involvement, and
- ✓ those with severe or life-threatening disease.

Stages (the steps) of in the treatment of vasculitis

I step

- Rapid suppression of the aggressive immune response in the disease onset - induction of remission.
- Induction of remission with a short course of aggressive treatment (adequate high doses of CST alone or in combination with cytotoxic immunosuppressors) - Cyclophosphamide, pulse-therapy, imunoglobulin i/v, extracorporeal methods, biological treatment.
- Rheological correction (fraxiparin, pentoxiphillin,, synthetic analogs of prostacyclin vazoprostan).

For 3 to 6 mo

- Steroids are given as daily oral prednisone (1 mg per kg, up to 60 mg daily).
- Pulsed intravenous steroids: methylprednisolone 1000 mg daily 3 days, can be given just before or with the first two intravenous pulses of cyclophosphamide. Cyclophosphamide can be administered as an intravenous infusion every two weeks (and later every three weeks), or as a daily low-dose oral treatment

II-d step

Long-term treatment (not less than 0.5 - 2 years), Maintenance therapy - Immunosuppressive therapy in doses sufficient to achieve clinical remission **(according disease activity)**

(During this period, the goal is to eliminate corticosteroids or reduce their dose and to use less potent immunosuppressants as long as needed.)

.

- Maintenance therapy with either azathioprine or methotrexate is initiated if remission has occurred after three to six months of induction therapy.
- Steroid dosage is tapered during this phase.
- Maintenance treatment for up to five years is recommended in patients with Wegener granulomatosis and patients who remain ANCA-positive. Some patients may require treatment indefinitely. Disease relapse may occur anytime after the remission.

III – d step

Treatment of relapse

- Achieving full and stable remission of the disease
- Determining the degree of target organ damage and correction of these injuries, rehabilitation.

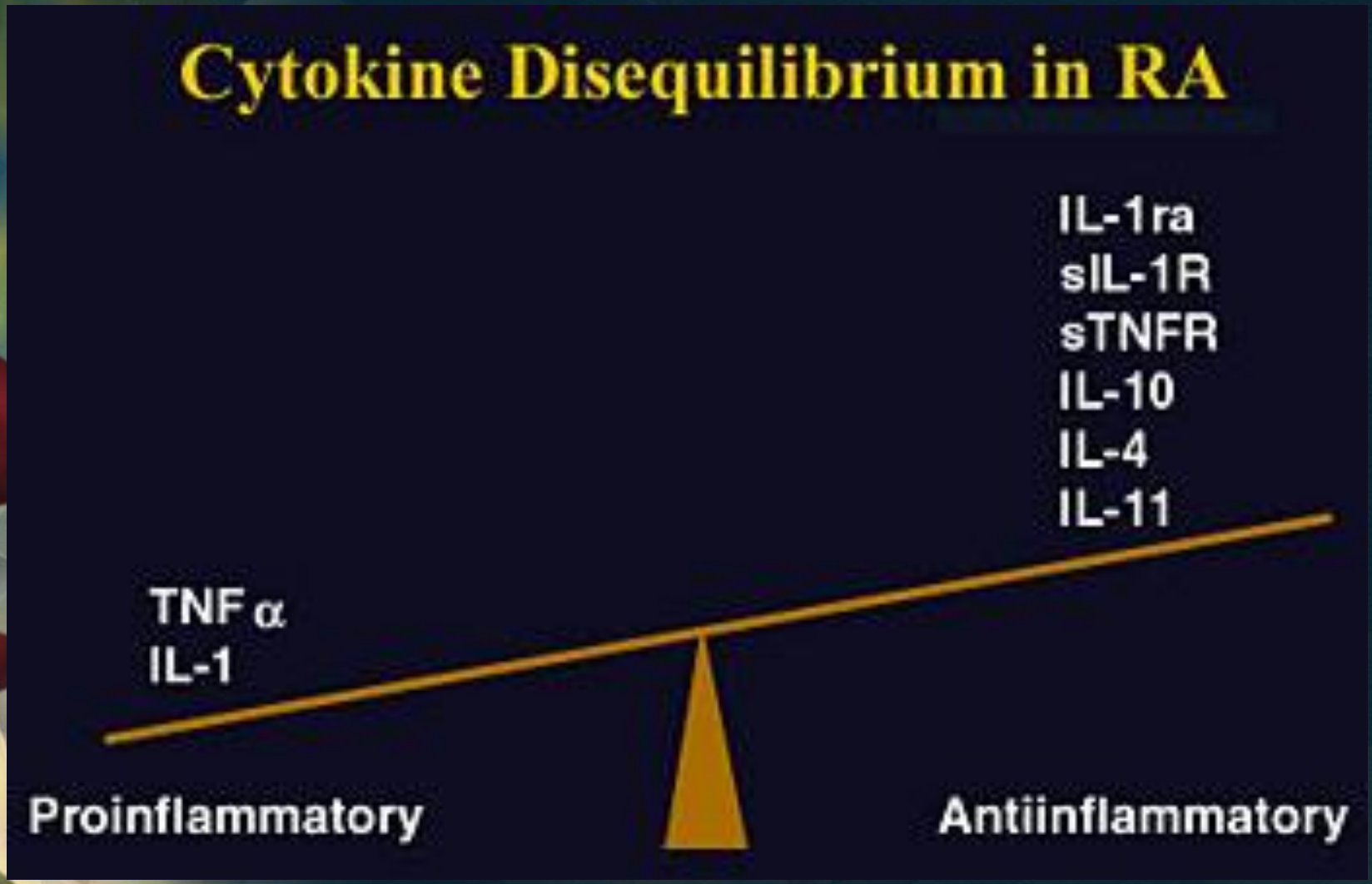
Summary of Drugs and Treatments Used for Systemic Vasculitis

- **Corticosteroids** (Prednisolone, Methylprednisolone)
- **Immunosupressors (**Cyclophosphamide**,** Azathioprine (Imuran), Methotrexat)
- **Mycophenolate mofetil** (CELLCEPT)
- **Agenţi biologici** (infliximab [Remicade**],** rituximab [Rituxan].
- **Intravenous immune globulin.**

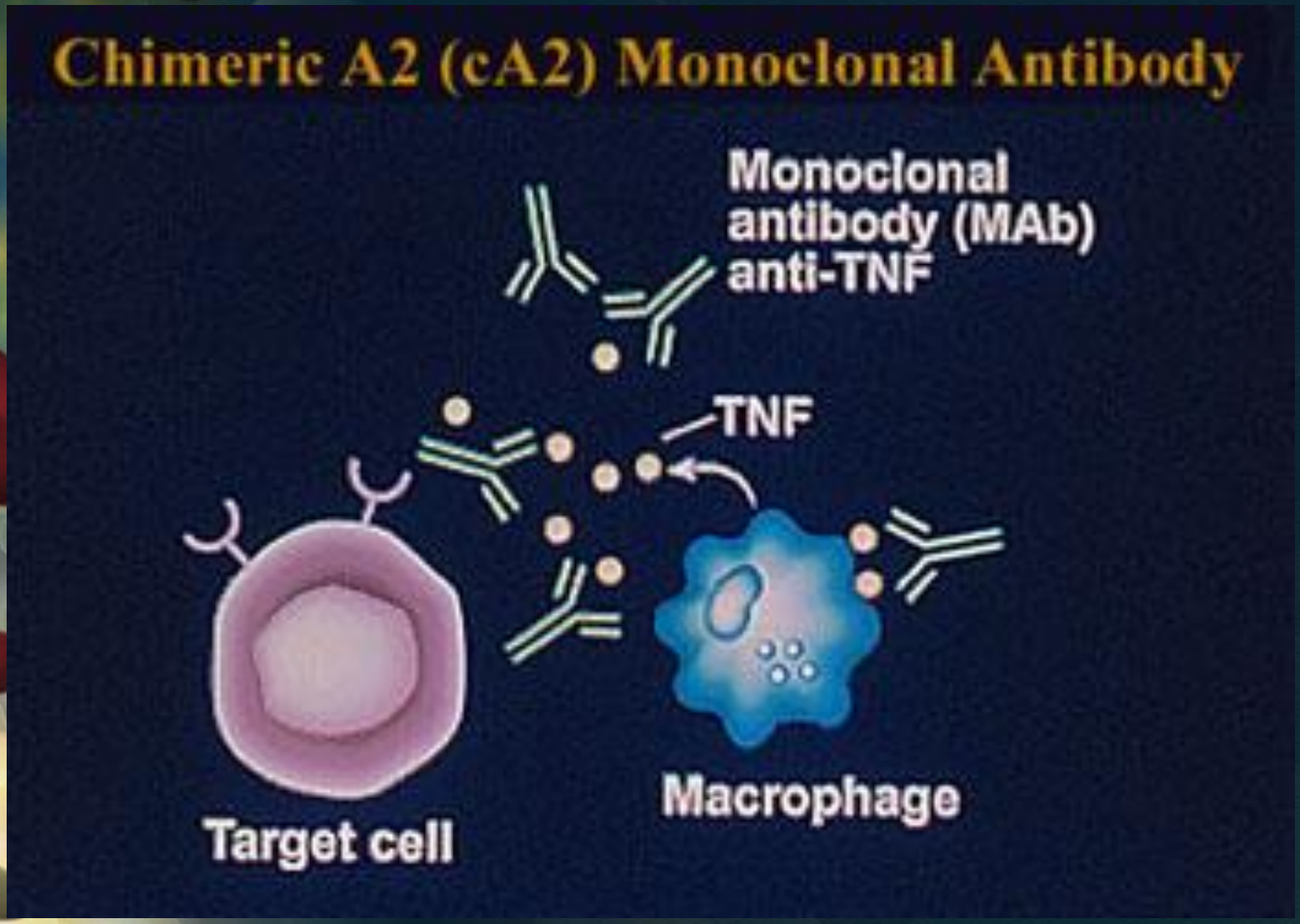
Anticytokine therapy

- **Himeric monoclonal antibodies directed against TNFα (Infleximab,)**
-
- **Etanercept (himeric TNF α receptors)**

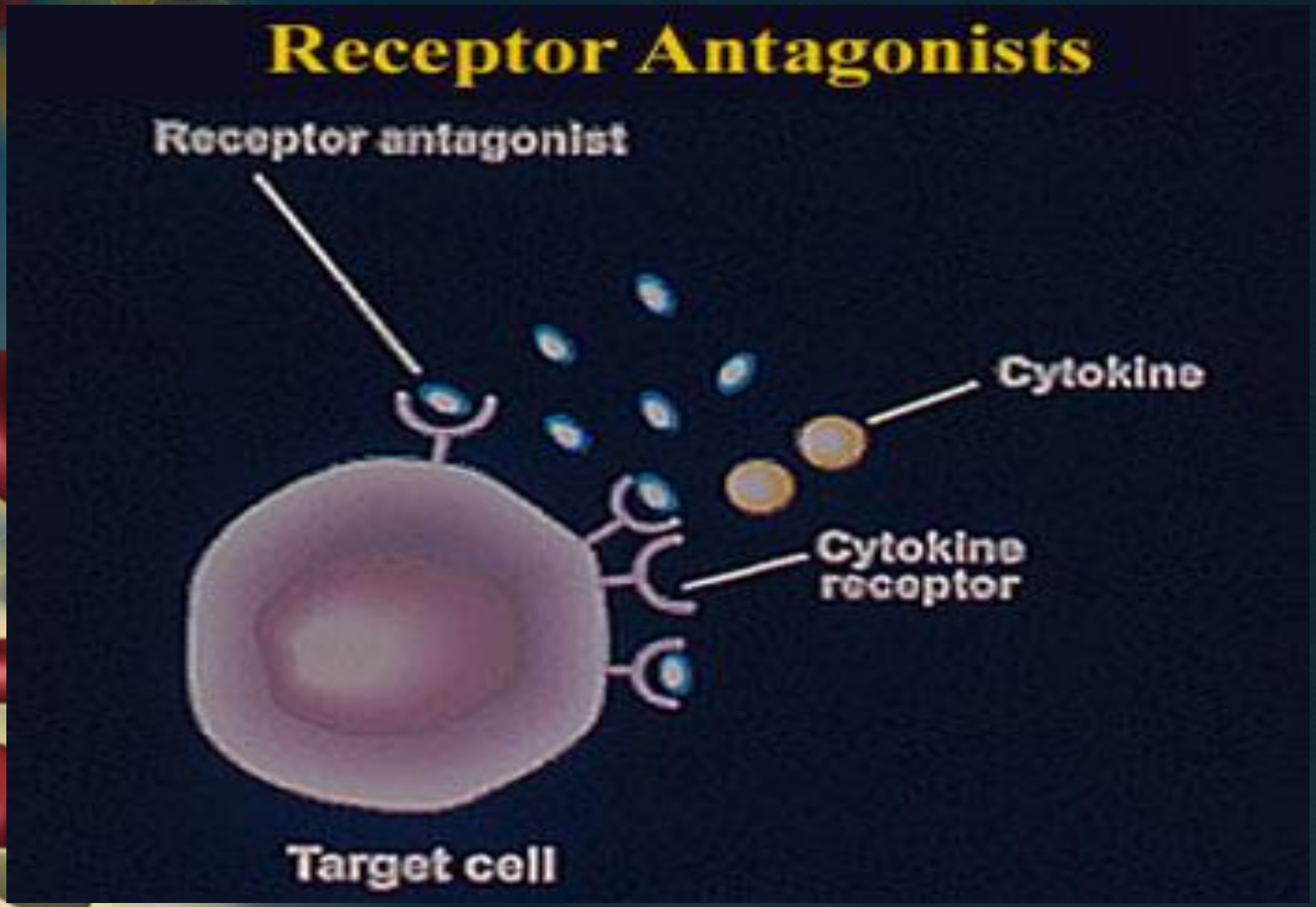
antiinflammatory cytokines (e.g., IL-4 and IL-10).



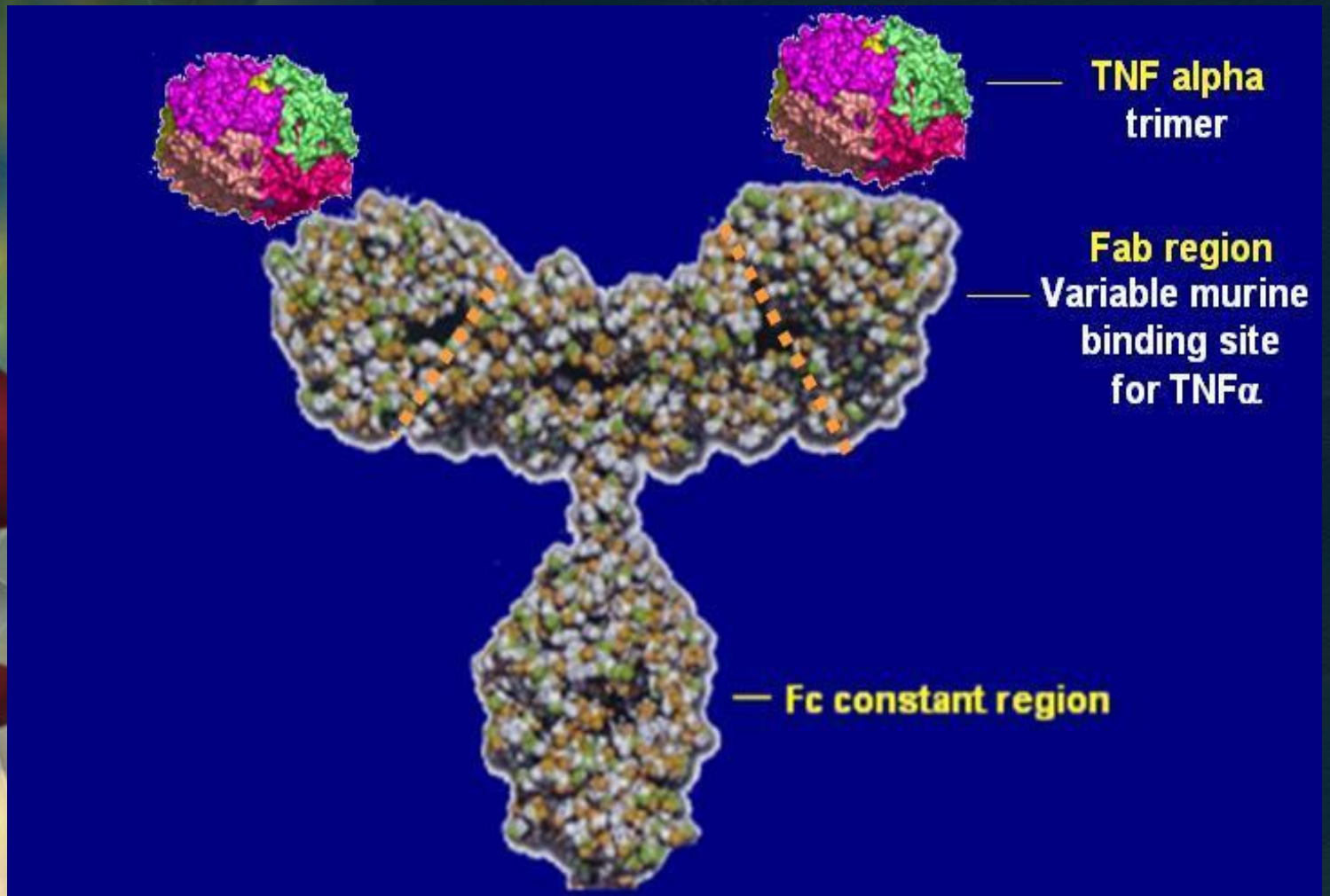
monoclonal antibodies directed against TNF or IL-1



antagonists of the TNF or IL-1 receptors



The anti-TNF-α monoclonal antibody infliximab is a major biological therapy for inflammatory bowel disease



Adapted from: Knight DM, *et al. Mal Immunol.* 1993; 30(16):1443-53.

Side effects and concerns

- Side effects of monoclonal antibodies.
- Early side effects include the risk of allergic reactions (including anaphylaxis which may be life-threatening), and reactions to the infusion.
- Risk of worsening infection, and can cause reactivation of old infections, like tuberculosis.
- Over time, there is the risk of serum sickness, which is a delayed hypersensitivity response to the medication.
- Later complications may include multiple sclerosis and lymphoma.
- Finally, the medication is quite expensive, with treatment costs ranging from US$3000 to $8000 per infusion.

Medium-sized vessels vasculitis

Poliarterita nodoasă (PAN)

- **Polyarteritis nodosa** (PAN) is a systemic vasculitis characterized by necrotizing inflammatory lesions that affect medium-sized and small muscular arteries (except the smallest- arterioles, capillaries, and venules), preferentially at vessel bifurcations, resulting in microaneurysm formation, aneurysmal rupture with hemorrhage, thrombosis, and, consequently, organ ischemia or infarction.
-

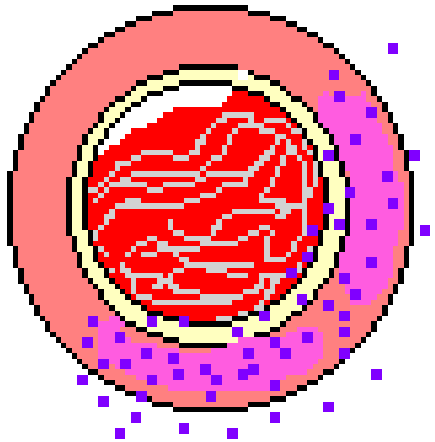
Polyarteritis Nodosa

Easy to diagnose and treat -- if you think of it.

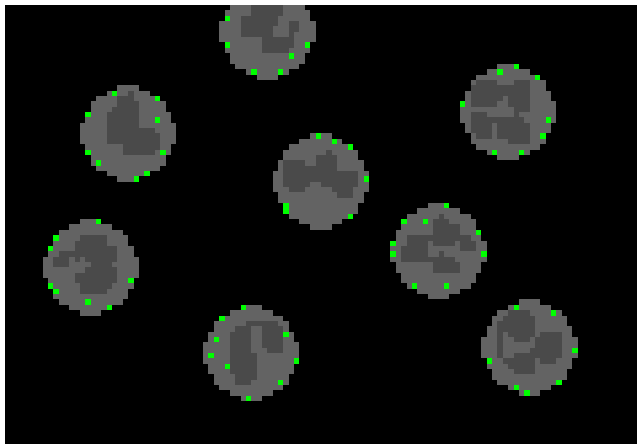
At least two types:

-- hepatitis immune vasculitis

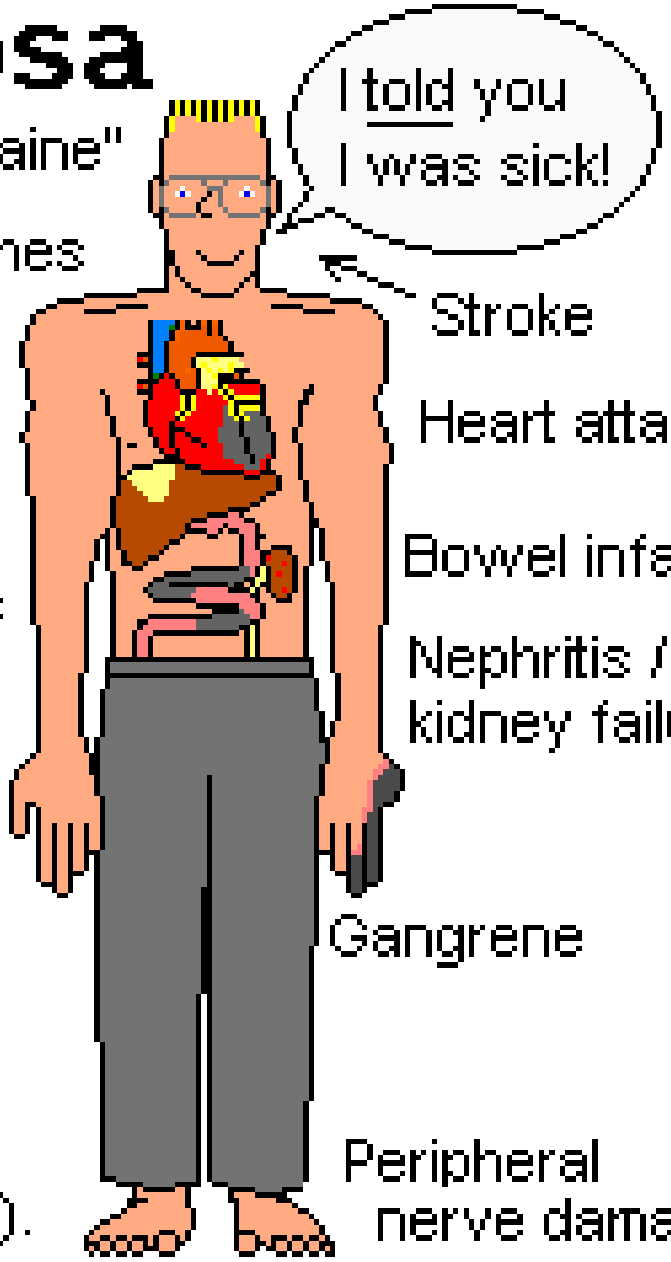
-- anti-neutrophil antibodies



Three-layer patchy vasculitis



Positive anti-neutrophil cytoplasm test (p-ANCA).



Epidemiology

- • The prevalence and annual incidence of PAN were estimated at 2 to 33 per million inhabitants.
- There is circumstantial evidence that PAN is associated with chronic hepatitis B virus infection, and this association is now well accepted (half of the patients diagnosed with PAN).
- PAN affects men more frequently than women (male-to-female ratio 2:1).
- PAN has been diagnosed in persons of every age; however, it is predominantly observed in individuals aged approximately 45-65 years.
-

A number of other infectious organisms have been reported in association with PAN, but causal evidence is inconsistent. These organisms include varicella-zoster virus, parvovirus B-19, cytomegalovirus, human T-cell leukemia virus, streptococcal species, *Klebsiella*, *Pseudomonas* species, *Yersinia* species, *Toxoplasma gondii*, Rickettsiae. Recently, reports of associations with PAN and human immunodeficiency virus and cutaneous PAN and tuberculosis have been published as well.

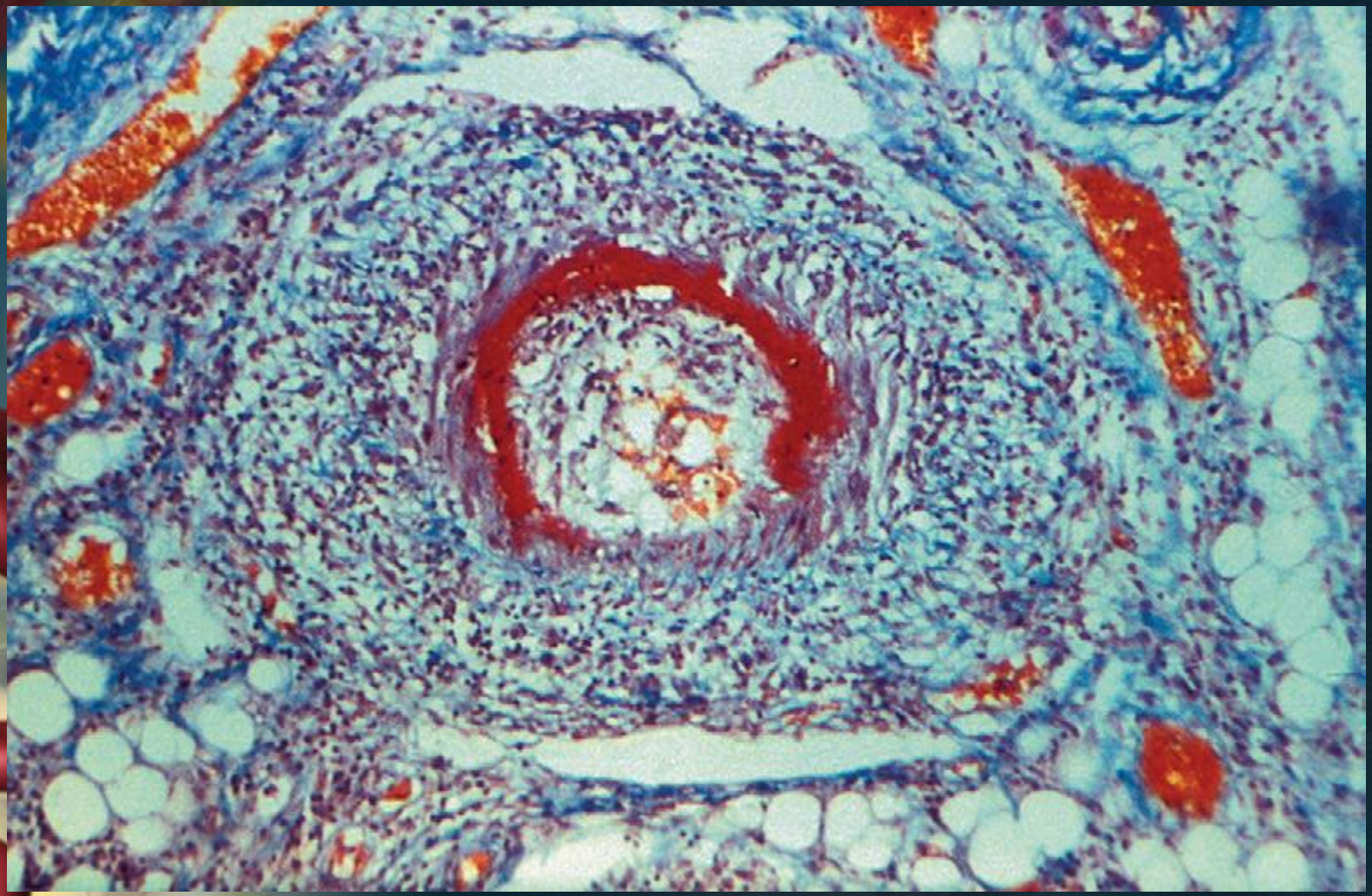
Pathogenesis

- ANCAs are generally absent;
- immune deposits are detected particularly in HBV-related PAN.
- In HBV-negative PAN, immune deposits are frequently absent and its immunopathogenesis is presently unclear.
- Deposits of immune complexes Ag-Ac → (immune complexes activate complement → stimulates the migration and activation of neutrophils)

Lesions develops in two stages:

- 1. inflammatory (acute) stage - polymorphic cellular infiltrate in the arterial wall associated with fibrinoid necrosis of the media. Inflammatory lesions can be complicated by thrombosis and aneurysms.
- 2. fibrotic (chronic) stage –
- repair injuries → endarteritis fibrous vascular occlusions

Medium-sized vessel arteritis in polyarteritis nodosa.



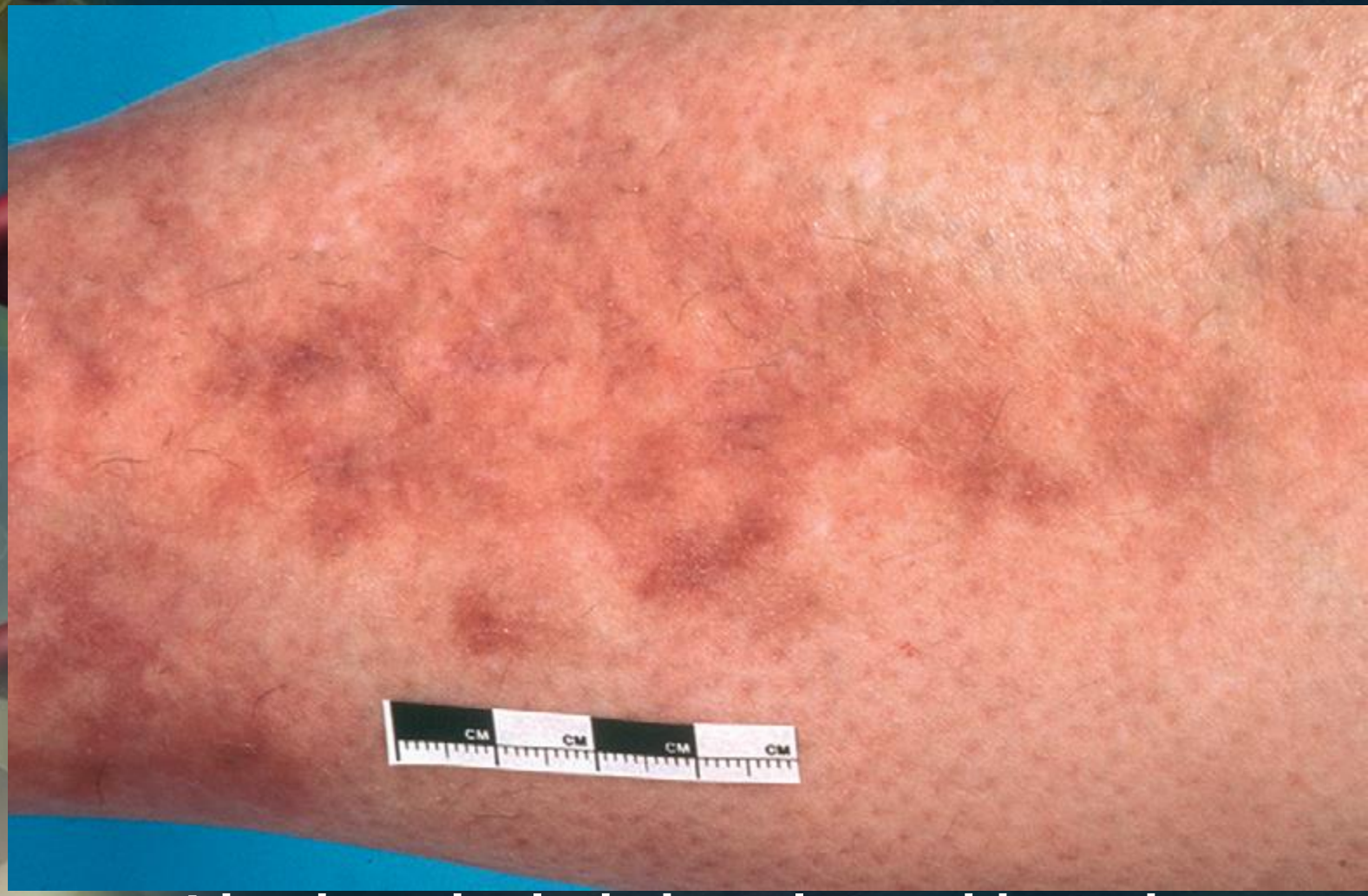
CLINICAL MANIFESTATIONS

- **The pathological process in PAN interests various organs but most commonly includes the skin, joints, peripheral nerves, bowel and kidneys.**

- **The pathological process in PAN interests various organs but most commonly includes the skin, joints, peripheral nerves, bowel and kidneys.**
- Typically, the patient experiences constitutional features of
- fever, malaise, weight loss, and diffuse aching, along with manifestations
- of multisystem involvement such as peripheral neuropathy and
- an asymmetric polyarthritis.

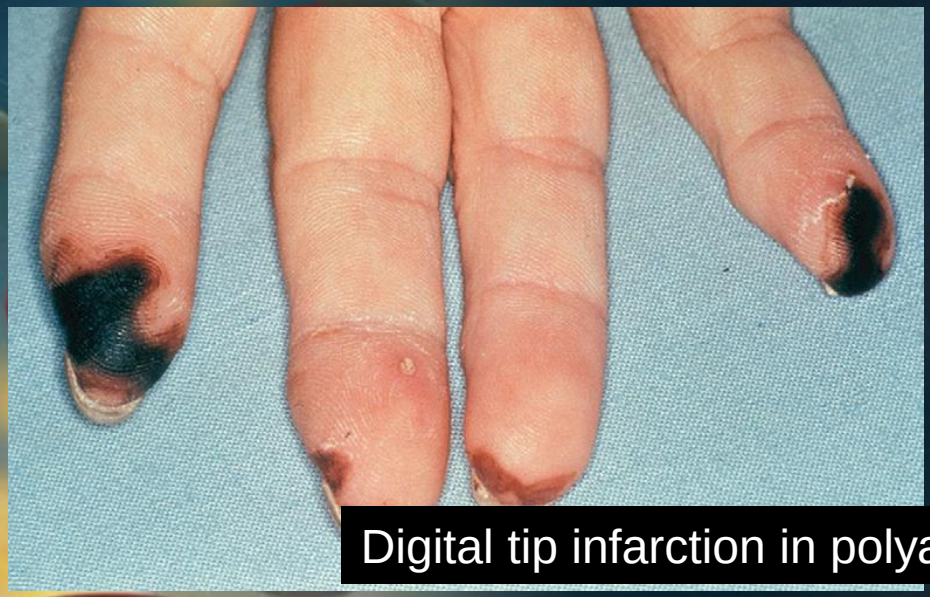
Cutaneous lesions

- **Cutaneous lesions**
- Cutaneous lesions include infarctions, ulcerations, livedo reticularis,
- subcutaneous nodules, and ischemic changes of the distal digits, and occur in 25% to 60% of patients.

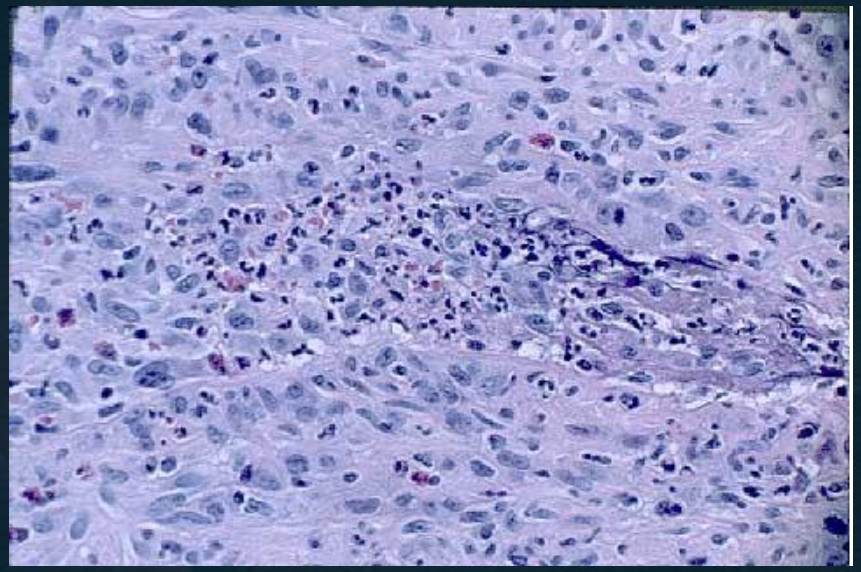


Livedo reticularis in polyarteritis nodosa.

- PAN is characterized by segmental necrotizing arterial lesions frequently with microaneurysm formation and resulting **in ischemia, infarction, and hemorrhage.**



Digital tip infarction in polyarteritis nodosa.



Multiple, tender, erythematous nodules and hyperpigmented circumferential plaques were present over the lower extremities.

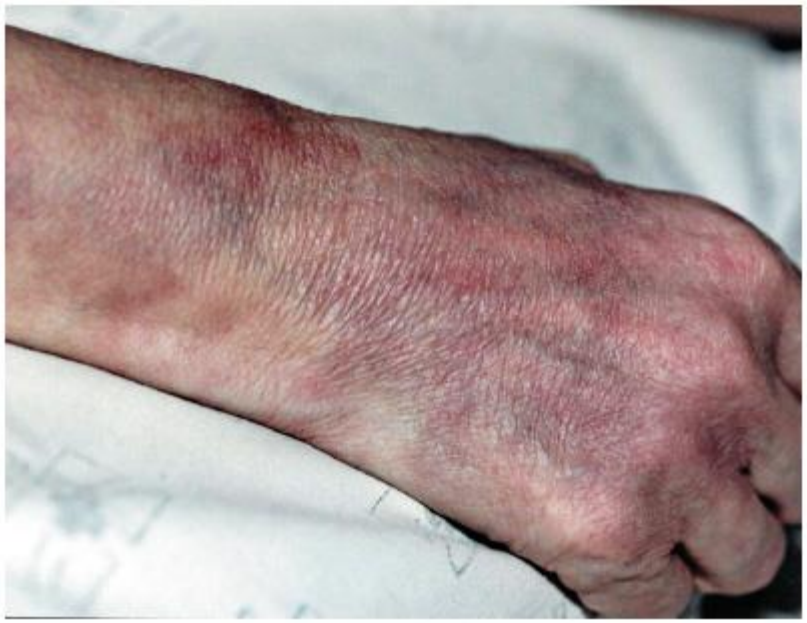


FIGURE 1: Intense livedo reticularis

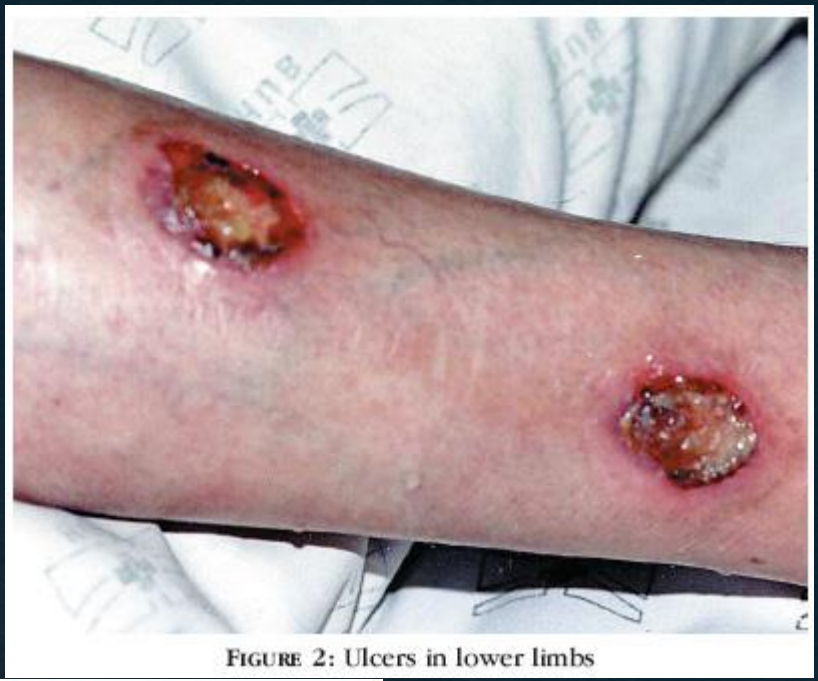


FIGURE 2: Ulcers in lower limbs

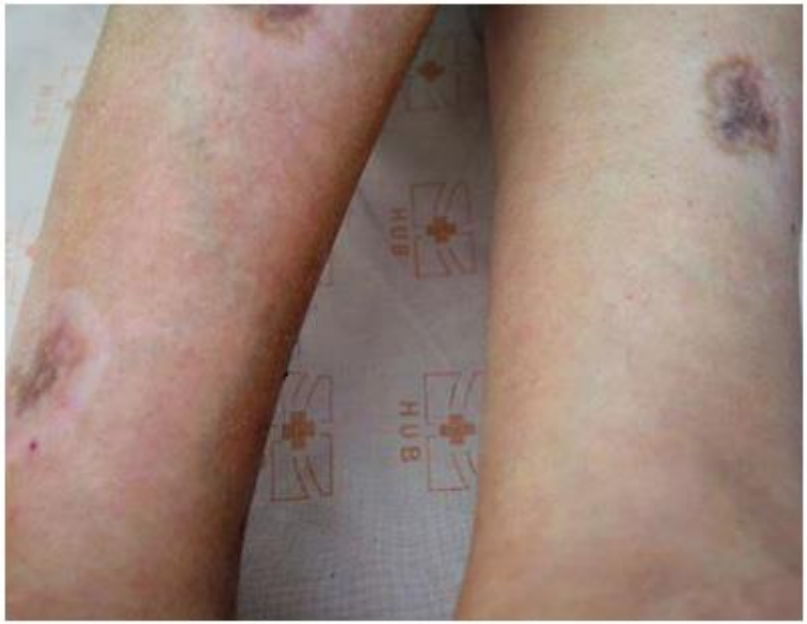
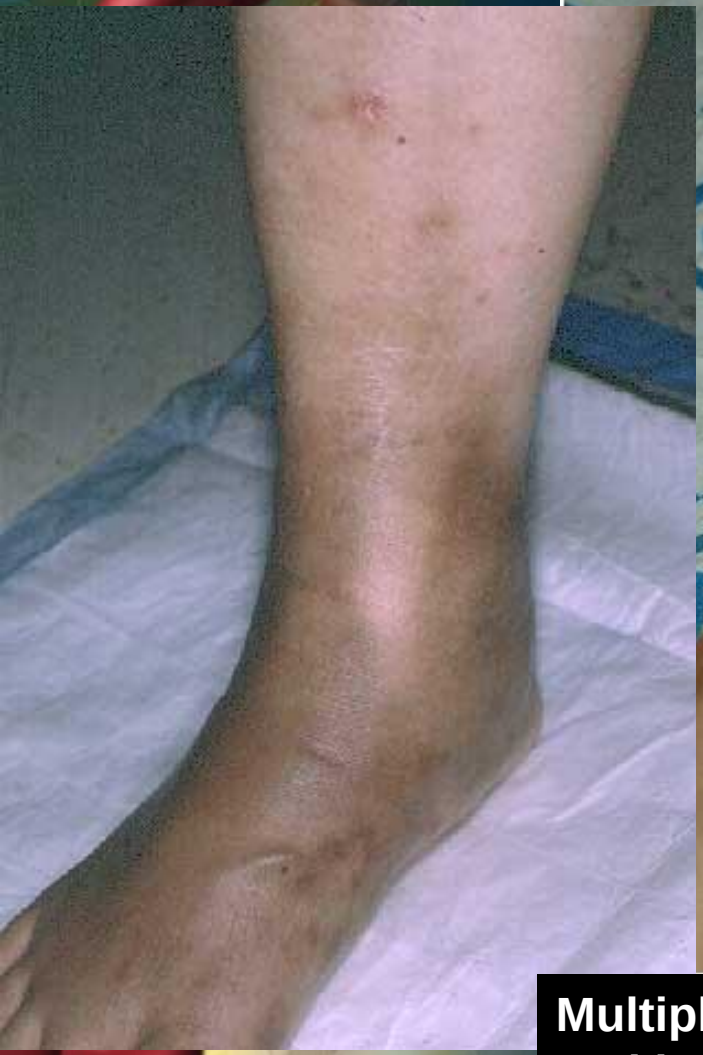
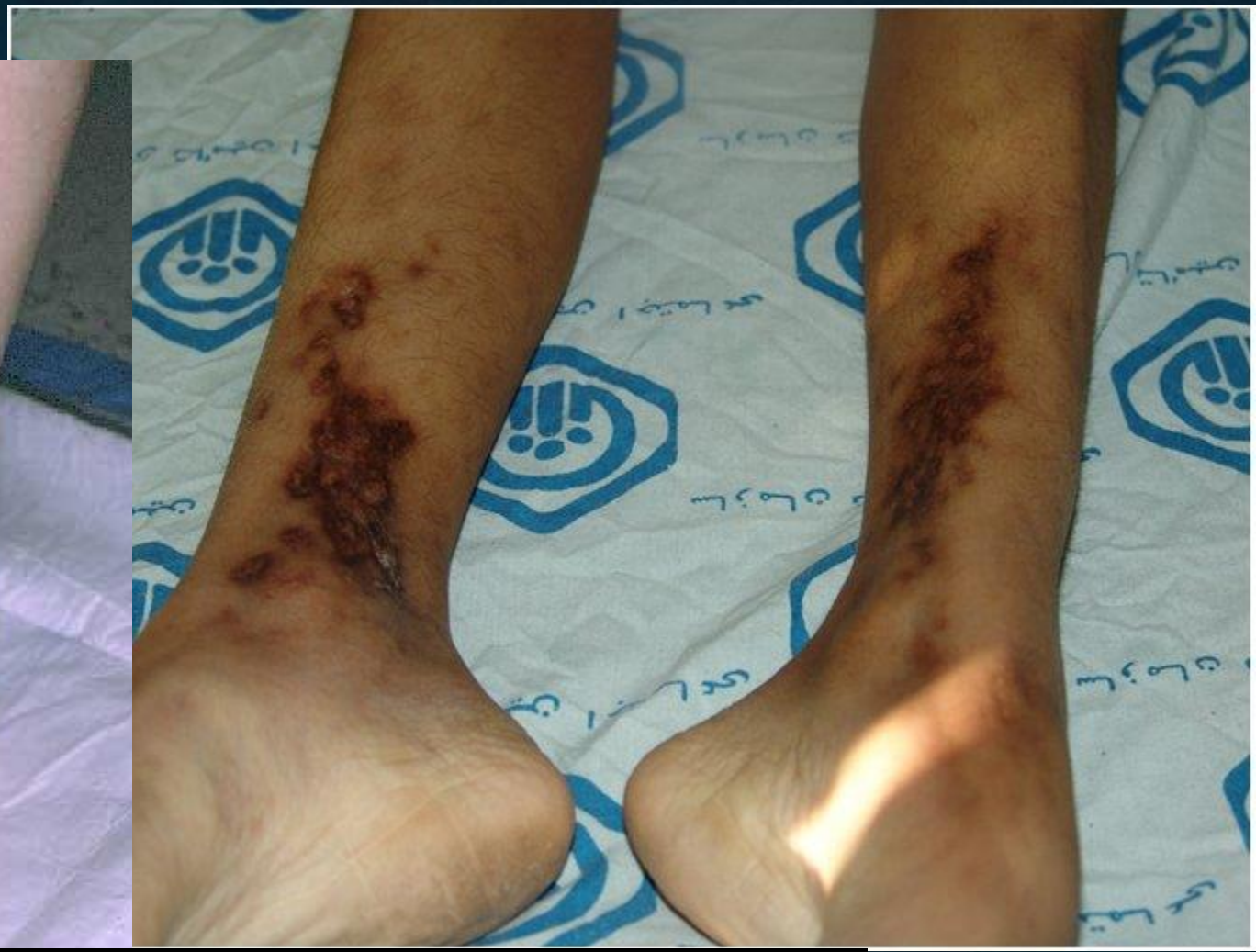


FIGURE 3: Hand after treatment with antibiotic therapy and cyclophosphamide





Multiple, tender, erythematous nodules and hyperpigmented circumferential plaques were present over the lower extremities.

Musculoskeletal features

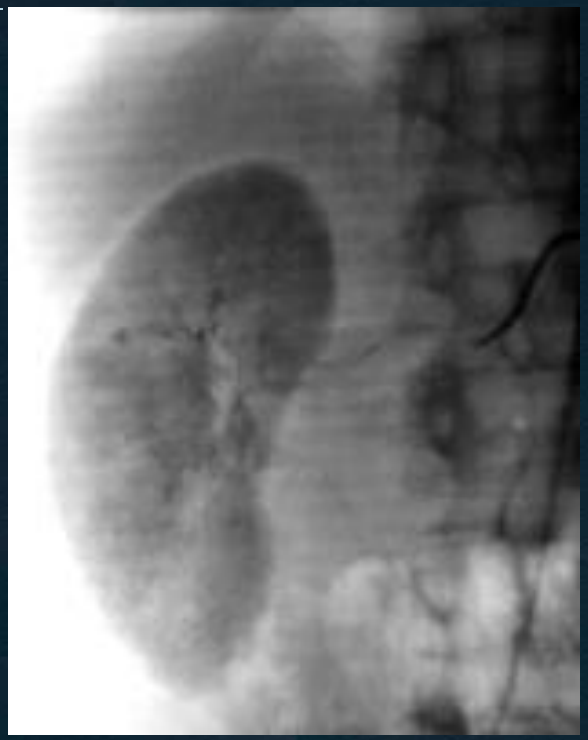
- Arthralgia or arthritis is present in as many as 50% of patients.
- An asymmetric, episodic, non-deforming polyarthritis involving the larger joints of the lower extremity may occur in up to 20% of cases, most commonly early in
- the disease.

Neurologic features

- Peripheral neuropathy may occur in up to 70% of PAN and may be the initial manifestation. The neuropathy affects the lower extremities.
- The onset is often very acute, with pain and paresthesias, with motor deficit, involve other peripheral nerves and produce mononeuritis multiplex or multiple mononeuropathy.
- Clinical manifestations suggestive of central nervous system (CNS) involvement are much less: headache, seizures, cranial nerve dysfunction, cerebral hemorrhage, and stroke.
-

Renal involvement

- is usually characterized by vascular nephropathy, without glomerulonephritis,
- in about 35% of patients.
- Multiple renal infarcts - the consequence of vascular nephropathy, produce renal failure. Renal angiography will frequently show several aneurysms and infarcts. Hypertension, usually mild, occurs in 21% to 33% of patients and is particularly associated with HBV infection.



- **Angiographic view of the right kidney demonstrates multiple intra-renal microaneurysms. Delayed images demonstrate residual contrast material within the aneurysms**

Cardiac involvement

- - is common pathologically but is recognized less often clinically.
- Myocardial infarction, when it occurs, is usually silent and is due to coronary arteritis
- Cardiomyopathy is predictive of increased mortality.

Gastrointestinal involvement

- Abdominal pain occurs in up to 70% of patients.
- Features of gastrointestinal

  involvement include abdominal pain, diarrhea, gut hemorrhage,

  and abnormal results of liver enzyme tests. Liver involvement is not common clinically, except if associated with hepatitis B.

Orchitis

- Testicular involvement is manifested by pain, but swelling or induration occurs only in a small percentage of patients.
- Is more common in vasculitis associated
- with hepatitis B. It is rarely the first manifestation of the disease, is usually unilateral, and is caused by ischemia of the testicular artery.

Other features

- Pulmonary involvement is uncommon in PAN.
- Diffuse involvement of skeletal muscle arteries may cause ischemic pain and intermittent claudication.
- Myalgias occur in about 50% of cases of polyarteritis, increased creatine kinase concentrations are unusual.
- Venous thromboembolism is less common 2.8% of patients.

LABORATORY TESTS AND ANGIOGRAPHY

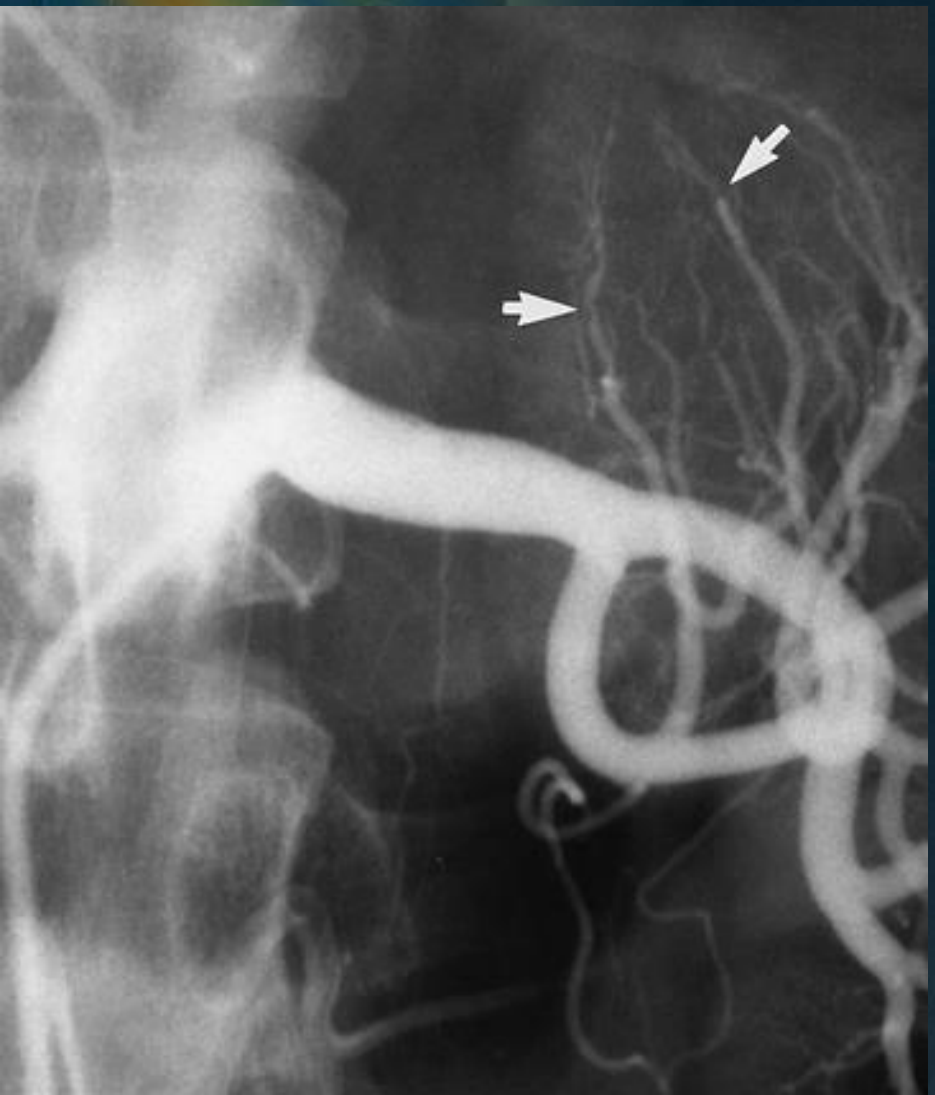
Non-specific inflammatory findings –

- increased erythrocyte sedimentation rate, and C-reactive protein,
- normochromic anemia, thrombocytosis,
- diminished concentrations of serum albumin.
- ANCAs are not present in PAN.
- HBsAg
- Rheumatoid factor, often associated with cryoglobulins.
- Low-titer antinuclear antibodies (not seen often).

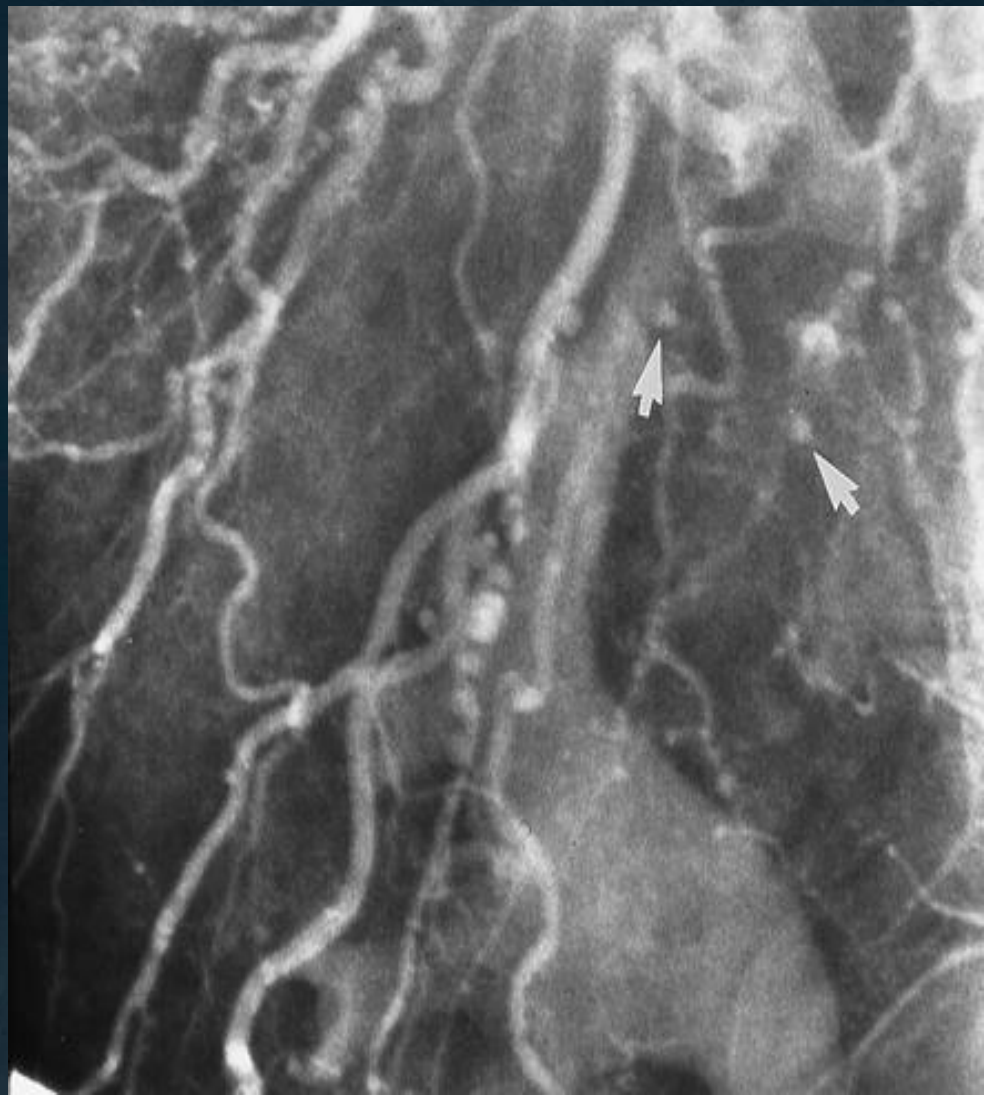
Angiography

- The angiogram may be the diagnostic procedure of choice PAN.
- The typical angiographic appearance includes **long segments of smooth arterial stenosis alternating with** areas of normal or dilated artery, smooth tapered
- **occlusions, thrombosis**, and the lack of significant atherosclerosis. The dilated segments include saccular and fusiform aneurysms, which strongly suggest PAN.

Stenosis of branches of left renal art.



II. Microanurysms in liver



The American College of Rheumatology (ACR) criteria for PAN

1. Weight loss of 4 kg or more
2. Livedo reticularis
3. Testicular pain/tenderness
4. Myalgia or leg weakness/tenderness
5. Mononeuropathy or polyneuropathy
6. Diastolic blood pressure greater than 90 mm/Hg
7. Elevated blood urea nitrogen (BUN) or creatinine level unrelated to dehydration or obstruction
8. Presence of hepatitis B surface antigen or antibody in serum
9. Arteriogram demonstrating aneurysms or occlusions of the visceral arteries
10. Biopsy of small- or medium-sized artery containing polymorphonuclear neutrophils

(In order for PAN to be diagnosed, at least 3 of the 10 ACR criteria should be present when radiographic or pathological diagnosis of vasculitis is made (sensibility 82,2% and specificity 86,6%).

Tratament

PAN non-associated with VHB

- **Corticosteroids**

Metilprednisolon 15 mg/kg/day (t in 60 min) 1-3 days

Prednisolon 1 mg/kg/day, in morning

The gradual reduction after improuvment.

Cyclophosphamide – association with CST only in severe evolution. Dose 0,5 g-2,5 g administrated 1-4 weeks. 912 mo).

Treatment

- Plasmapheresis – in PAN refractory
- Complementary Therapy:

- Analgezics
- IECA
- prevention of side effects of immunosuppressive terapy

Rheological therapy

Treatamen

PAN associate with VHB

- CST and immunosupressors are contraindicated.
- Interferon alfa – 2 b, lamivudina, baraclude et al.)
- Plasmapheresis
- Cura scurta de corticosteriozi poate fi indicata initial pentu controlul manifestarilor acute,severe, urmat de sevraj busc