Revmatologický ústav

Spektrum vaskulitid

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EFFECT OF CYCLOPHOSPHAMIDE UPON THE IMMUNE RESPONSE IN WEGENER'S GRANULOMATOSIS

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Abstract Nine patients with Wegener's granulomatosis were studied before and after treatment with cyclophosphamide alone. The study was undertaken to determine any immunologic abnormalities associated with the disease, to observe the effect of cyclophosphamide on the clinical course, as well as on the immune response in man, and to observe any correlation between clinical response and immunosuppression. Untreated patients had elevated mean serum IgA levels of 470 as compared with 200 mg per 100 ml in normal controls and elevated mean parotid-fluid secretory IgA levels of 4.7 as compared with 1.8 mg per 100 ml in normal controls. Seven of nine patients receiving cyclophosphamide had undetectable humoral and delayed hypersensitivity responses to a new antigenic stimulus, and five of the seven retained previously established delayed hypersensitivity. A favorable clinical response to cyclophosphamide and immunosuppression appeared to be correlated.

The Spectrum of Vasculitis

Clinical, Pathologic, Immunologic, and Therapeutic Considerations

Moderator: ANTHONY S. FAUCI, M.D., F.A.C.P. *Discussants:* BARTON F. HAYNES, M.D.; and PAUL KATZ, M.D.; Bethesda, Maryland

Vasculitis is a clinicopathologic process characterized by inflammation and necrosis of blood vessels. Certain disorders have vasculitis as the predominant and most obvious manifestation, whereas others have various degrees of vasculitis in association with other primary disorders. Within the entire spectrum of vasculitis virtually any size or type of blood vessel in any organ system can be involved. Most of the vasculitides can be associated directly or indirectly with immunopathogenic mechanisms. In this regard, immune complex mediation is being increasingly recognized as the underlying mechanism in several of the vasculitides. With clinical, pathologic, and immunologic criteria, certain vasculitic disorders can be clearly recognized and categorized as distinct entities, whereas in others there is an overlap of different diseases within a broader category. In recent years, several of the more serious vasculitides, such as Wegener's granulomatosis and the systemic necrotizing vasculitides of the polyarteritis nodosa group, which formerly had extremely poor prognoses, have been shown to be extraordinarily responsive to chronic low-dose cytotoxic therapy, particularly cyclophosphamide.

DR. ANTHONY S. FAUCI (Head, Clinical Physiology Section, Laboratory of Clinical Investigation, Deputy Clinical Director, National Institute of Allergy and Infectious Diseases): Vasculitis is a clinicopathologic process characterized by an inflammation and necrosis of blood vessels. It can exist as the major and primary manifestation of a number of clinical syndromes, or it may represent a relatively minor component of other primary disease processes.

Necrotizing vasculitis was first described more than 100 years ago in a 27-year-old man by Kussmaul and Maier (1). That patient had what is now called classic polyarteritis nodosa. With this early description, all vasculitides were originally thought to be polyarteritis nodosa. However, it soon became clear that the disseminated vasculitides comprised a broad spectrum of disorders involving vessels of different types, sizes, and locations characterized by various clinical manifestations, with or without identifiable precipitating factors. In many cases, attempts at classification of the vasculitides into separate categories either resulted in an oversimplified grouping or a cumbersome series of categorizations with little appreciation of overlap. Such approaches were of little consequence at a time when identification of precipitating antigens was not feasible, and the few available therapeutic modalities were generally ineffective.

The following discussions will focus on recent advances in the appreciation of the pathogenesis, immunologic mechanisms, and clinical manifestations of several of these diseases, leading to a clearer understanding of the distinctions and overlaps among these disorders and, most importantly, to more rational and directed therapeutic approaches resulting in striking remissions and improved prognosis in several heretofore devastating diseases.

Pathophysiology and Immunologic Mechanisms

It has now become clear that a substantial proportion of the necrotizing vasculitides are either directly caused by, or closely associated with, immunopathogenic mechanisms. Also, as advanced technology becomes progressively more available, it is likely that offending antigens and immunologic phenomena will be directly associated with virtually all of the vasculitides. In this regard, it is reasonable to extrapolate an immunopathogenisis or association from certain diseases with well-established immunopathogenesis to that spectrum of vasculitides with suggestive, but less definitive, immunopathogenesis. For example, systemic vasculitis is an important clinicopathologic feature of several of the connective tissue or collagen vascular diseases, such as systemic lupus erythematosus and rheumatoid arthritis, in which immunopathogenic mechanisms are well established (2-6). Additionally, clear-cut immunopathogenesis has been established in several of the primary vasculitides, particularly in cases of hepatitis B antigen-associated necrotizing vasculitis

► An edited transcription of a Combined Clinical Staff Conference at the Clinical Center, Bethesda, Maryland, 2 February 1978, by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health, Education, and Welfare.

► Authors who wish to cite a section of this conference and specifically indicate its author can use this example for the form of reference:

HAYNES BF: Treatment of the granulomatous vasculitides, pp. 671-673 in FAUCI AS (moderator): The spectrum of vasculitis. Clinical, pathologic, immunologic, and therapeutic considerations. *Ann Intern Med* 89 (Part 1):660-676, 1978

Historické spektrum vaskulitid

Polyarteritis nodosa group of systemic necrotizing vasculitis
Classic polyarteritis nodosa
Allergic granulomatosis
Systemic necrotizing vasculitis—"overlap syndrome"
Hypersensitivity vasculitis
Subgroups of hypersensitivity vasculitis
Serum sickness and serum-sicknesslike reactions
Henoch-Schönlein purpura
Essential mixed cryoglobulinemia with vasculitis
Vasculitis associated with malignancies
Vasculitis associated with other primary disorders
Wegener's granulomatosis
Lymphomatoid granulomatosis
Giant-cell arteritides
Temporal arteritis
Takayasu's arteritis
Thromboangiitis obliterans (Buerger's disease)
Mucocutaneous lymph node syndrome
Miscellaneous vasculitides

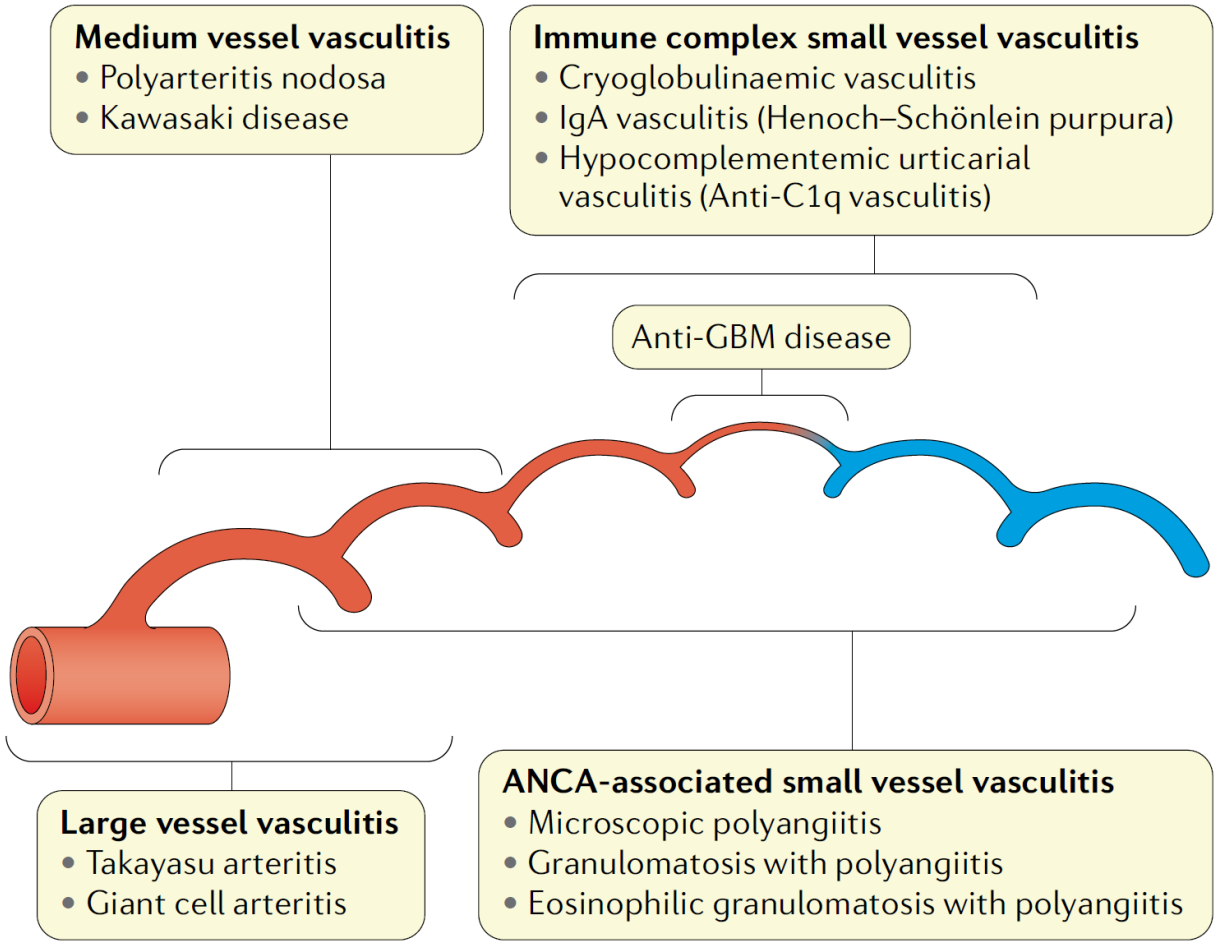
1. hypersenzitivní angiitida
2. alergická granulomatózní angiitida
3. revmatická arteritida
4. periarteritis nodosa
5. temporální arteritida

Fauci AS, Haynes B, Katz P. Ann Intern Med. 1978 Nov;89(5 Pt 1):660-76

Zeek PM. Am J Clin Pathol. 1952 Aug;22(8):777-90.

Revidovaná klasifikace vaskulitid

Chapel Hill Consensus Conference (CHCC 2012)



Primární vaskulitidy

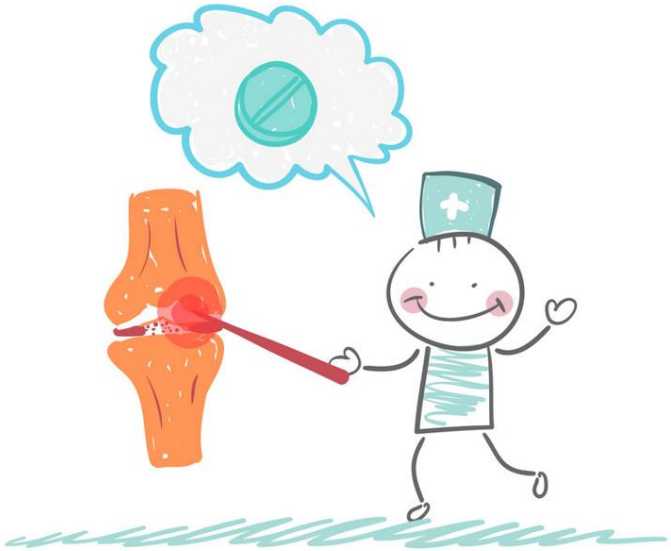
Sekundární vaskulitidy

Jennette JC, et al. Arthritis Rheum. 2013 Jan;65(1):1-11.

Neexistuje univerzální klasifikační systém velikosti cév

	Small vessels	Medium vessels	Large vessels
Chapel Hill 2012 nomenclature [3](i)	Intraparenchymal arteries, arterioles, capillaries, venules, and veins	Main visceral arteries and veins and their initial branches	Aorta and its major branches and analogous veins
Cardiovascular pathology viewpoint [4]	Arterioles, capillaries, venules	Small- and medium-sized arteries throughout the body (including both distributing and intraparenchymal arteries)	Aorta and aortic arch branches, distributing arteries of the extremities and neck
Dermatopathology viewpoint [5•]	Arterioles, capillaries, post-capillary venules (found both in the dermis and subcutis)	Small arteries or small veins (diameter <800 µm, four to eight medial muscular layers without distinct tunica adventitia) found in the subcutis or dermal-subcutis junction	(not present in skin)
Neuroradiology viewpoint [6](ii)	Cerebral arteries with lumen diameter < 0.75 mm (e.g., lenticulostriate artery)	Cerebral arteries with lumen diameters of 0.75–2.0 mm (M3/4-, A2-5, and P2-5- segments of middle, anterior and posterior cerebral arteries; posterior inferior, anterior inferior and superior cerebellar arteries; M2- and A1/P1-segments are usually also considered medium sized)	Internal carotid, vertebral and basilar artery, M1-segment of middle cerebral artery
Daily practice (rheumatology) (iii)	Arterioles, capillaries, venules, small intraparenchymatous Arteries and veins (e.g., retinal arteries with diameter of approximately 0.15 mm)	Remaining muscular arteries and corresponding veins (including splanchnic and renal vessels)	All elastic arteries and "large" distributing muscular arteries and corresponding veins (aorta, main pulmonary, Brachiocephalic, common/internal carotid, vertebral, subclavian, axillary, brachial, common and external/internal iliac, femoral, popliteal)

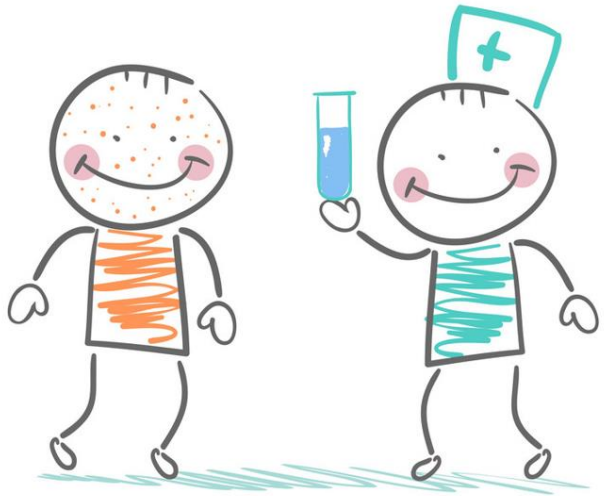
Seitz L, et al. Curr Rheumatol Rep. 2022 Nov;24(11):352-370.



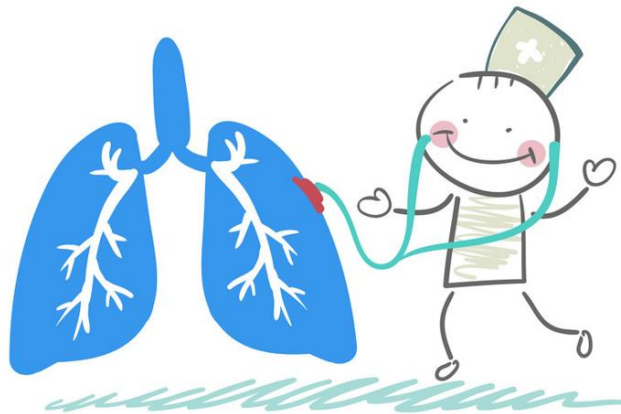
rheumatologist

immunologist

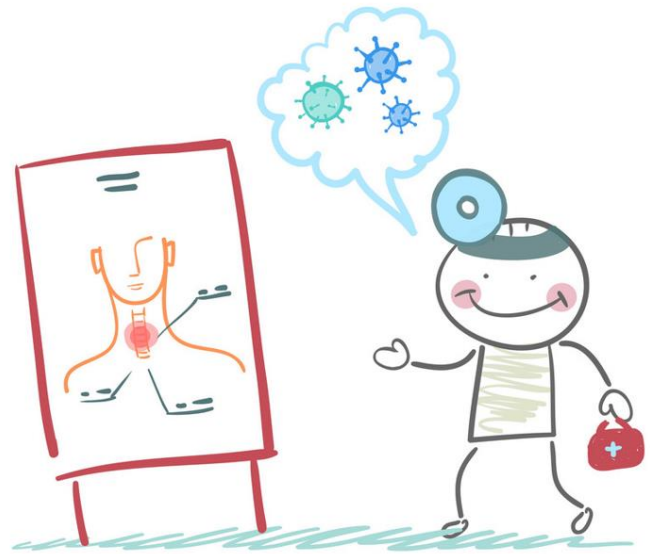
pathologist



dermatologist



pulmonologist

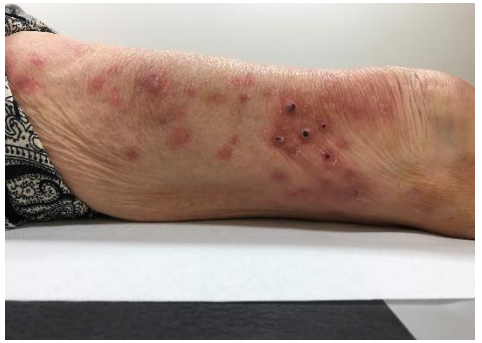


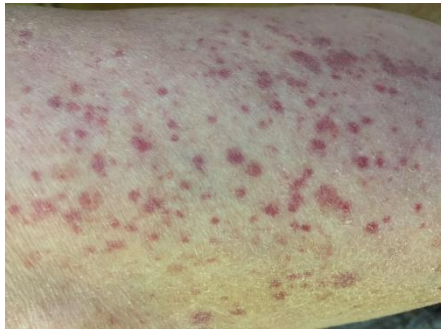
otolaryngologist

Spektrum kožních vaskulitid

1) Imunokomplexové vaskulitidy
2) ANCA asociované vaskulitidy

- **Idiopatická LCV ~ 50 % případů**
- **Hypersenzitivní vaskulitidy - polékové a postinfekční ~ 40 %**
- Vaskulitidy u systémových onemocnění
- Vaskulitidy asociované s malignitami
- IgA vaskulitida, urtikariální a kryoglobulinemická vaskulitida





Chen KR, Carlson JA. Am J Clin Dermatol. 2008;9(2):71-92.
Seitz L, et al. Curr Rheumatol Rep. 2022 Nov;24(11):352-370.

Spektrum sekundárních vaskulitid velkých a středních cév

- Systémová onemocnění pojiva a artritidy
- IgG4 asociovaná onemocnění (aorta, 10 - 35 %)
- Chronická periaortitida
- Relabující polychondritida, VEXAS
- Autoinflammatorní onemocnění (monogenní, polygenní)
- Primární imunodeficience (CVID – 2 %, Wiskott-Aldrichův syndrom, 1-29 %)
- Malignity a paraneoplastické projevy (hematologické malignity, koincidence...)
- Léky indukované vaskulitidy (TNFi, vakcíny, inhibitory kontrolních bodů, filgrastim, ...)
- Infekce (stafylokoky, streptokoky, HBV, HCV, VZV, P19, EBV, SARS-CoV-2,...)
- Vaskulitické mimikry

Lötscher F, et al. Curr Rheumatol Rep. 2022 Oct;24(10):293-309.

Vaskulitidy u revmatických onemocnění

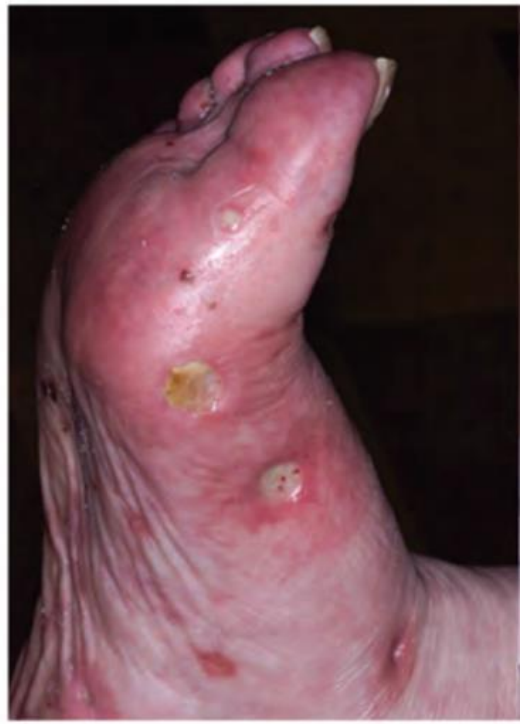
- SLE - nejčastěji kožní leukocytoklastická vaskulitida (90 %)
  - vzácně „PAN-like“ (extrémně vzácně „TAK-like“)

- Sjögrenův syndrom - nejčastěji kožní leukocytoklastická vaskulitida (>95 %)
  - kryoglobulinemická vaskulitida
  - vzácně „PAN-like“

Lötscher F, et al. Curr Rheumatol Rep. 2022 Oct;24(10):293-309.

Revmatoidní vaskulitida

- Dlouhotrvající RA (>10 let trvání)
- Deformující, často vyhaslá RA
- Revmatická nodulóza
- RF/ACPA pozitivita
- Komorbidity
- Feltyho syndrom
- Plicní fibróza



Organ system	Clinical presentation
Skin (most common)	Purpura
	Nail fold infarcts
	Digital ischemia/gangrene
	Cutaneous ulcers (upper or lower extremity)
Peripheral nervous system	Mononeuritis multiplex
	Distal asymmetric/symmetric sensory and/or mixed polyneuropathy
Eye	Episcleritis
	Scleritis (anterior/posterior, nodular/diffuse, nonnecrotizing/necrotizing scleromalacia perforans)
	Peripheral ulcerative keratitis (with or without corneal melt)
	Retinal vasculitis
Heart	Pericarditis
	Myocarditis (presenting as arrhythmias – atrial fibrillation, ventricular arrhythmias and complete heart block)
	Coronary vasculitis (presenting as myocardial infarction)
Lung	Pulmonary angiitis/capillaritis (presenting as alveolar hemorrhage)
Kidney	Pauci-immune glomerulonephritis
	Medium vessel vasculitis (without microaneurysms)
Gastrointestinal tract	Mesenteric vasculitis
	Bowel (commonly ileal or sigmoid) ischemia and/or perforation
Central nervous system	Hypertrophic pachymeningitis
	Central nervous system vasculitis (presentations include seizures, cranial nerve palsies, strokes and myelopathy)

Makol A, et al. Curr Opin Rheumatol. 2015 Jan;27(1):63-70.

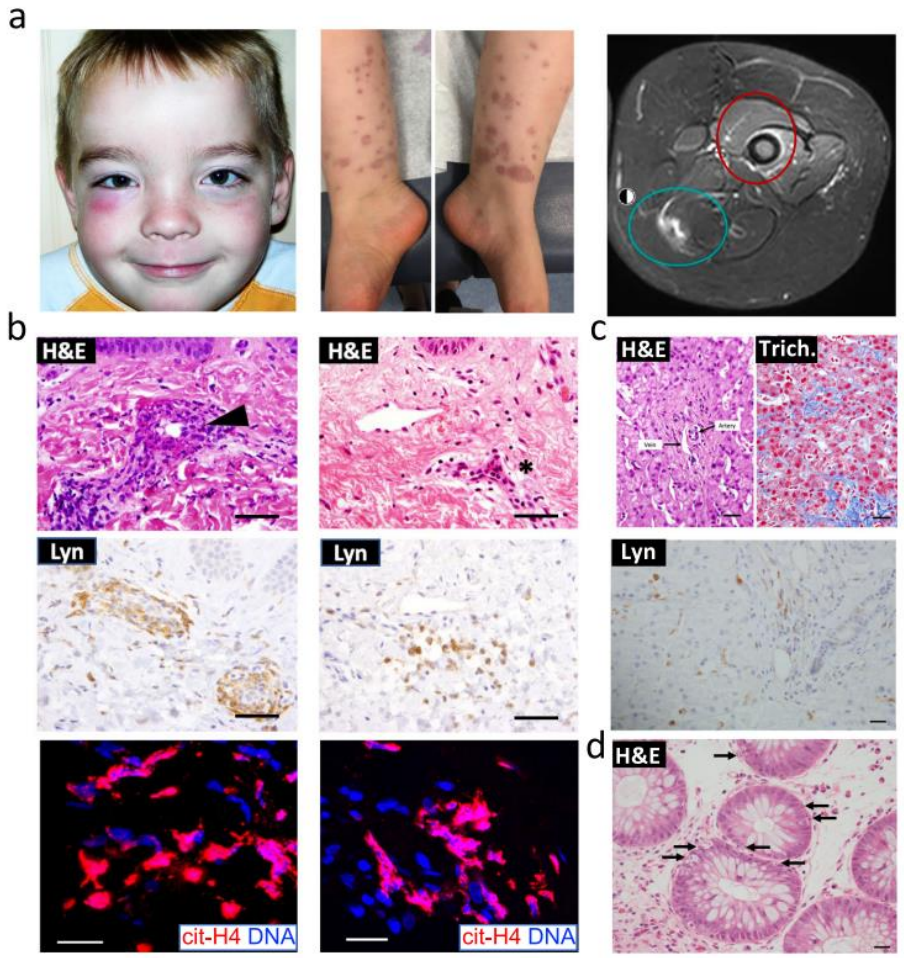
LAVLI – nové autoinflamatorní onemocnění

„Lyn kinase-associated vasculopathy and liver fibrosis“

- de novo aktivační mutace Lyn kinázy

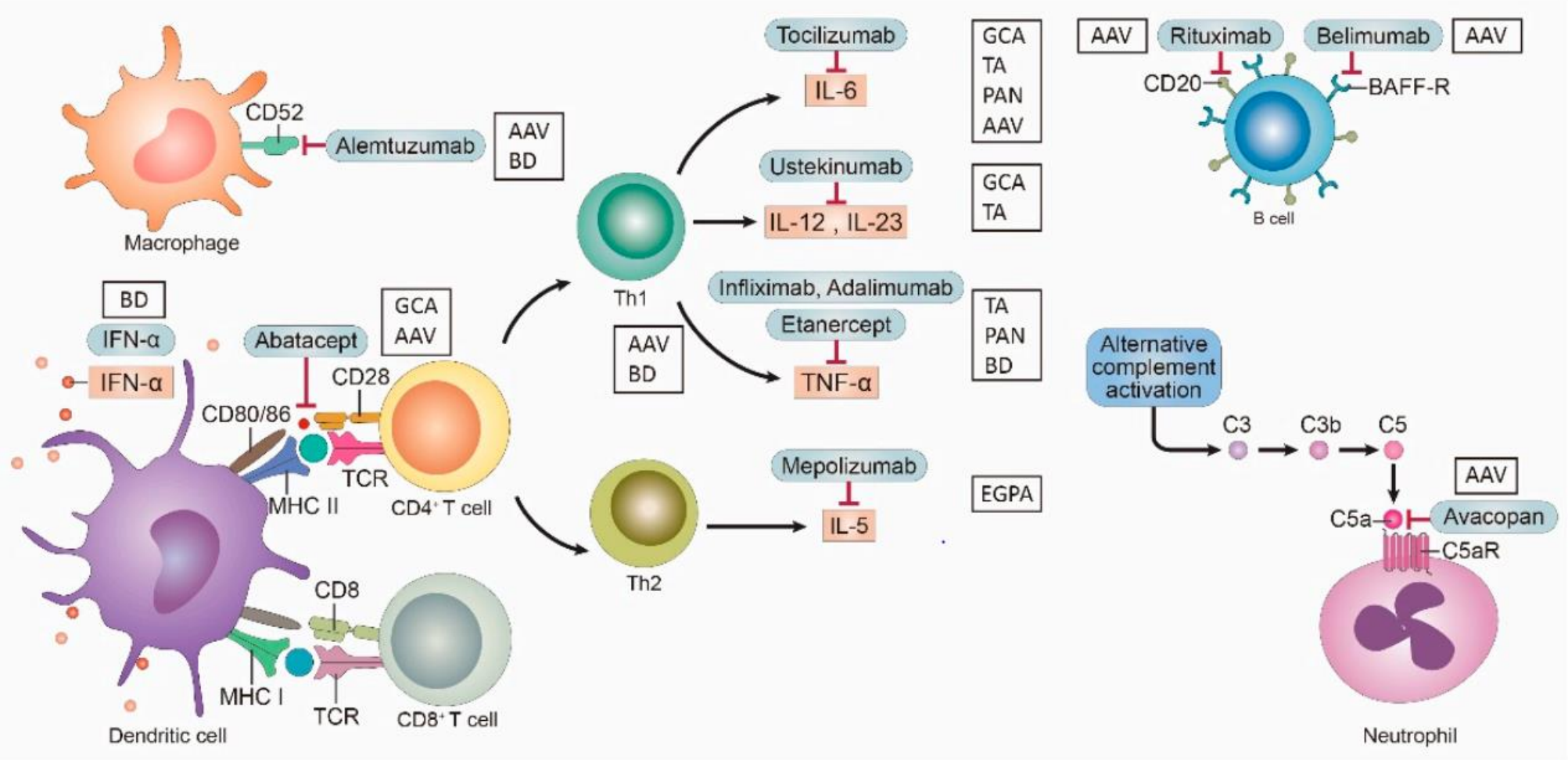
1. kožní vaskulitida malých cév
2. fibrotizace jater
3. systémový zánět

- TNFi a dasatinib (Src kinázový inhibitor)



de Jesus AA, et al. Nat Commun. 2023 Mar 17;14(1):1502.

Spektrum možných léčebných cílů u vaskulitid



Chung SW. Biomedicines. 2021 Jun 30;9(7):757.