Od fibrózy k MOF

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

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Fibrosis — A Common Pathway to Organ Injury and Failure

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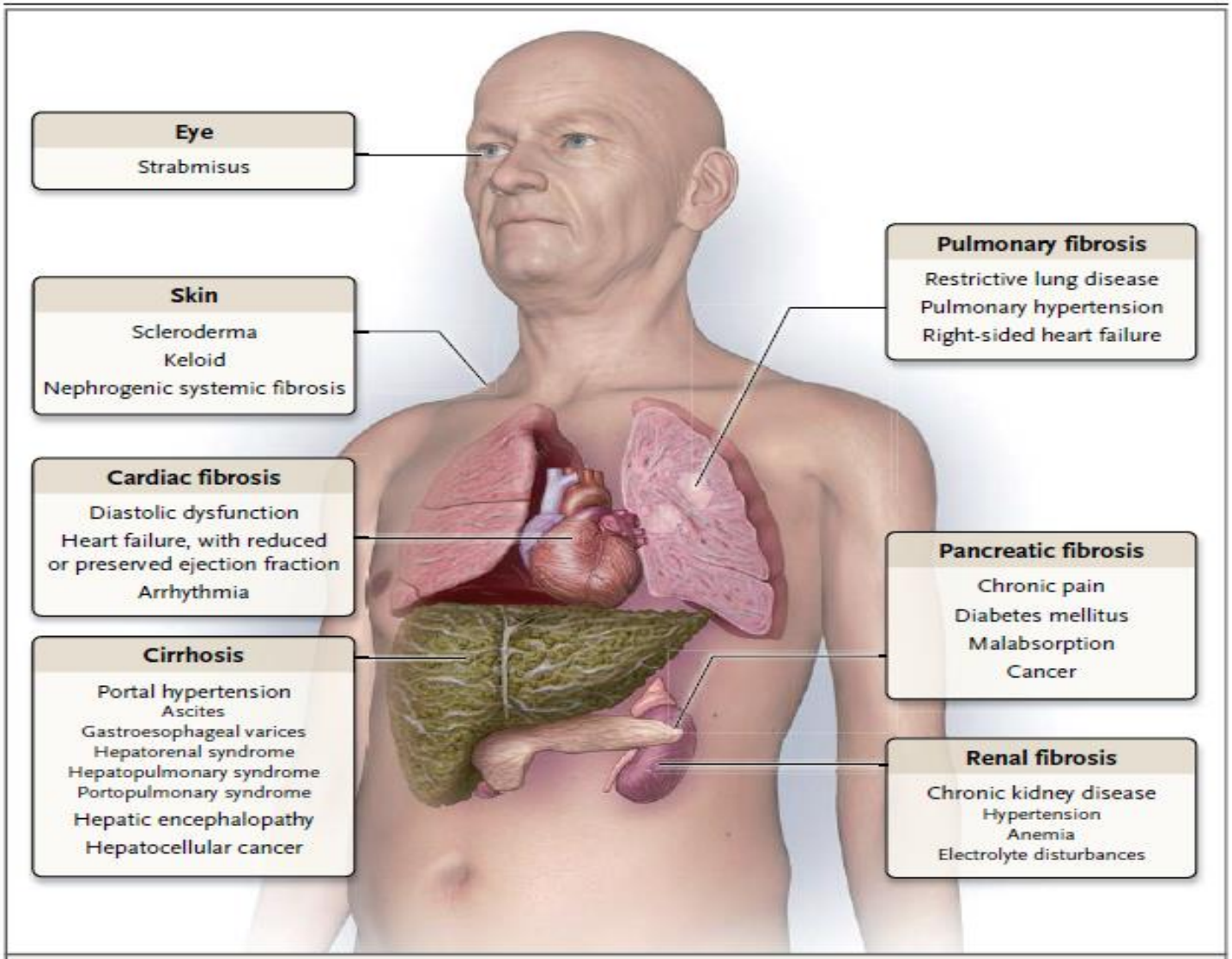


Figure 1. Fibrogenesis and Major Organ Systems.
Fibrosis is a pathologic feature of disease in virtually all organs. It has protean and often lethal consequences and accounts for substantial morbidity and mortality. Selected organs and associated diseases are highlighted.

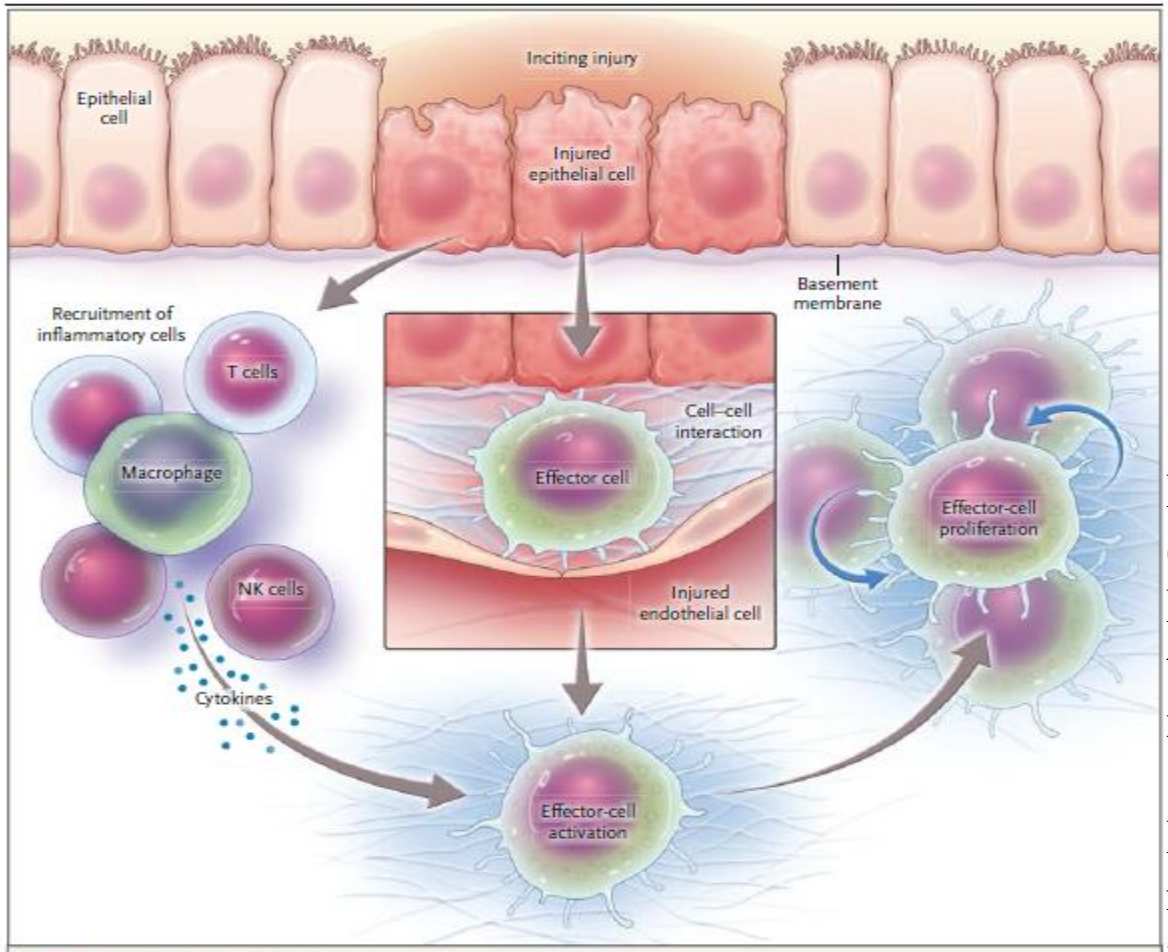


Figure 2. Cellular Injury and Fibrogenesis.
In parenchymal organs, many different types of stimuli lead to epithelial-cell injury (top), which is typically followed by an inflammatory response (shown at left). This process stimulates a fibrogenic wound-healing response that involves multiple cellular and molecular systems. At the cellular level, the recruitment of inflammatory cells is central. Inflammatory cells produce a variety of mediators, cytokines, and other factors that are responsible for the stimulation and recruitment of other cells. Key among these cells are fibrogenic effector cells; these cells are of mesenchymal origin and include fibroblasts, fibrocytes, tissue-specific pericytes and myofibroblasts, and fibroblasts derived through epithelial-to-mesenchymal transition. These effectors produce a variety of extracellular matrix proteins, which themselves may modify the wound milieu, often stimulating fibrogenic effector cells in an autocrine fashion. Indeed, in most organ systems, autocrine loops in fibrogenic effector cells are prominent. Cell–cell interactions lead to further activation of effector cells. Effector cells produce a variety of extracellular matrix proteins, peptides, cytokines, and growth factors, all of which may lead to autocrine stimulation (see the right side of the figure), typical of most organ systems. Many forms of injury also lead to the activation and transformation of other cells, such as specialized endothelial or tissue-specific cells. Injury to these cells in turn leads to a variety of downstream effects, including activation of fibrogenic effector cells. NK denotes natural killer.

Klíčové jsou fibrogenní efektorové buňky mesenchymálního Původu – fibroblasty, fibrocyty, tkánově specifické pericyty a myofibroblasty

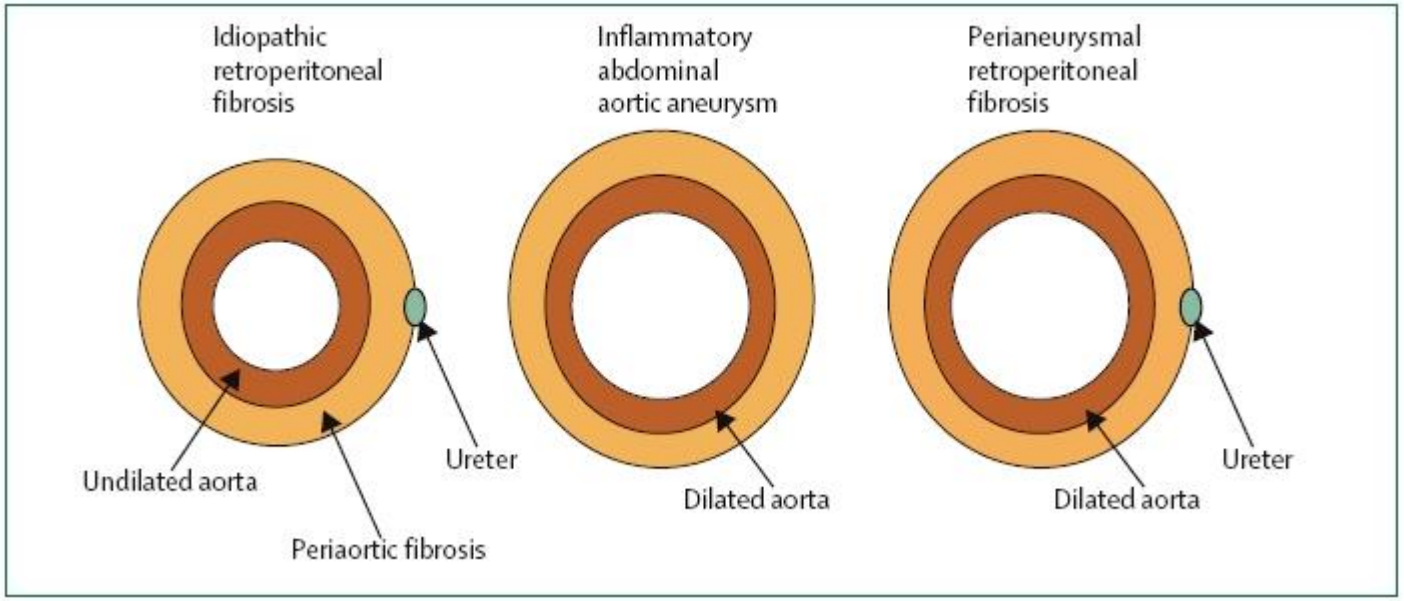
Produkce extracelulárních matrixových proteinů, které stimulují fibrogenní buňky k autokrinní produkci

IgG4 asociovaná onemocnění

- IgG4-related sclerosing cholangitis
- Mikulicz's disease (IgG4-related dacryoadenitis and sialadenitis)
- Sclerosing sialadenitis (Küttner's tumor, IgG4-related submandibular gland disease)
- Inflammatory orbital pseudotumor (IgG4-related orbital inflammation or orbital inflammatory pseudotumor)
- Chronic sclerosing dacryoadenitis (lacrimal gland enlargement, IgG4-related dacryoadenitis)
- A subset of patients with "idiopathic" retroperitoneal fibrosis (Ormond's disease) and related disorders (IgG4-related retroperitoneal fibrosis, IgG4-related mesenteritis)
- Chronic sclerosing aortitis and periaortitis (IgG4-related aortitis or periaortitis)
- Riedel's thyroiditis (IgG4-related thyroid disease)
- IgG4-related interstitial pneumonitis and pulmonary inflammatory pseudotumors (IgG4-related lung disease)
- IgG4-related kidney disease (including tubulointerstitial nephritis [TIN] and membranous glomerulonephritis [GN] secondary to IgG4-RD)
- IgG4-related hypophysitis
- IgG4-related pachymeningitis

Ormond disease

characterized by fibroinflammatory tissue surrounding the abdominal aorta and the iliac arteries
An estimated incidence 1,38/100 000



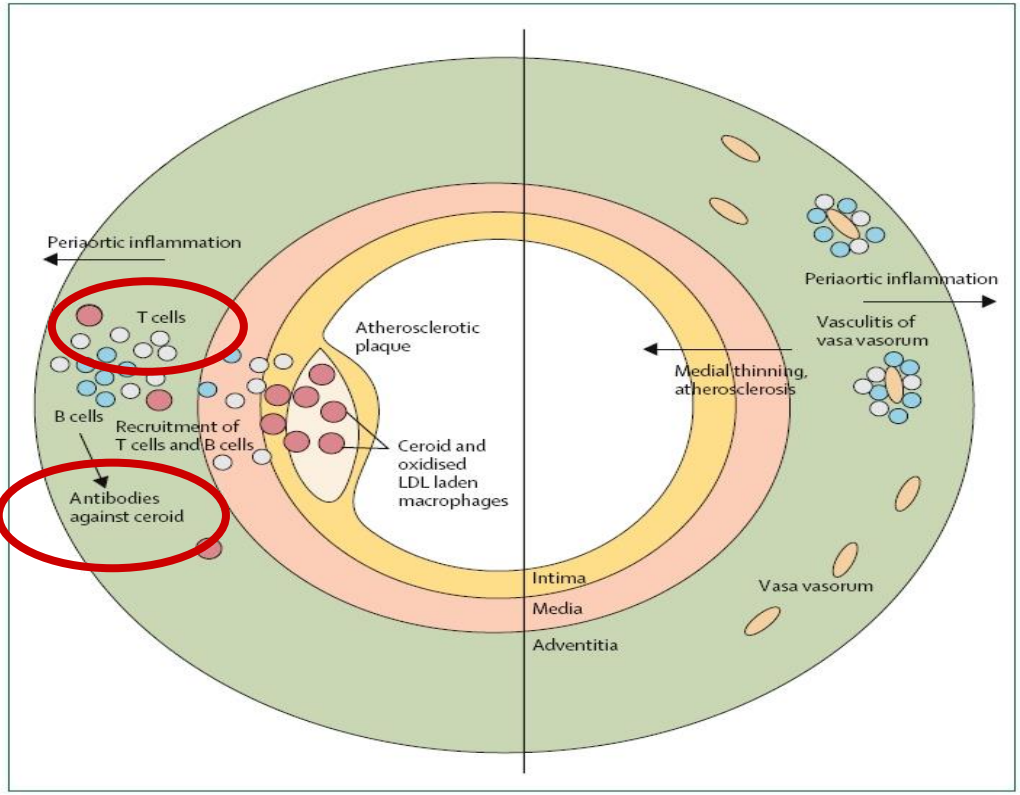


Figure 2: Two potential pathogenetic mechanisms of chronic periaortitis

Left of vertical line: hypothesis of autoallergic aortitis presented—atherosclerotic plaque macrophages elaborate antigens, such as oxidised LDL and ceroid, and present them to immunocompetent cells, such as B lymphocytes and T lymphocytes. These are recruited and activated in medial and adventitial aortic layers. B cells produce antibodies to ceroid, which are found in close apposition to extracellular ceroid. The inflammatory reaction then extends into the periaortic retroperitoneum.

Right of vertical line: chronic periaortitis is initiated in adventitia, with an inflammatory involvement of vasa vasorum; a vasa vasorum vasculitis is often seen in chronic periaortitis. This inflammatory process can cause weakening of aortic wall with medial thinning and promote atherosclerosis, and also extend into surrounding retroperitoneum.

Radiografické nálezy u Mb. Ormond

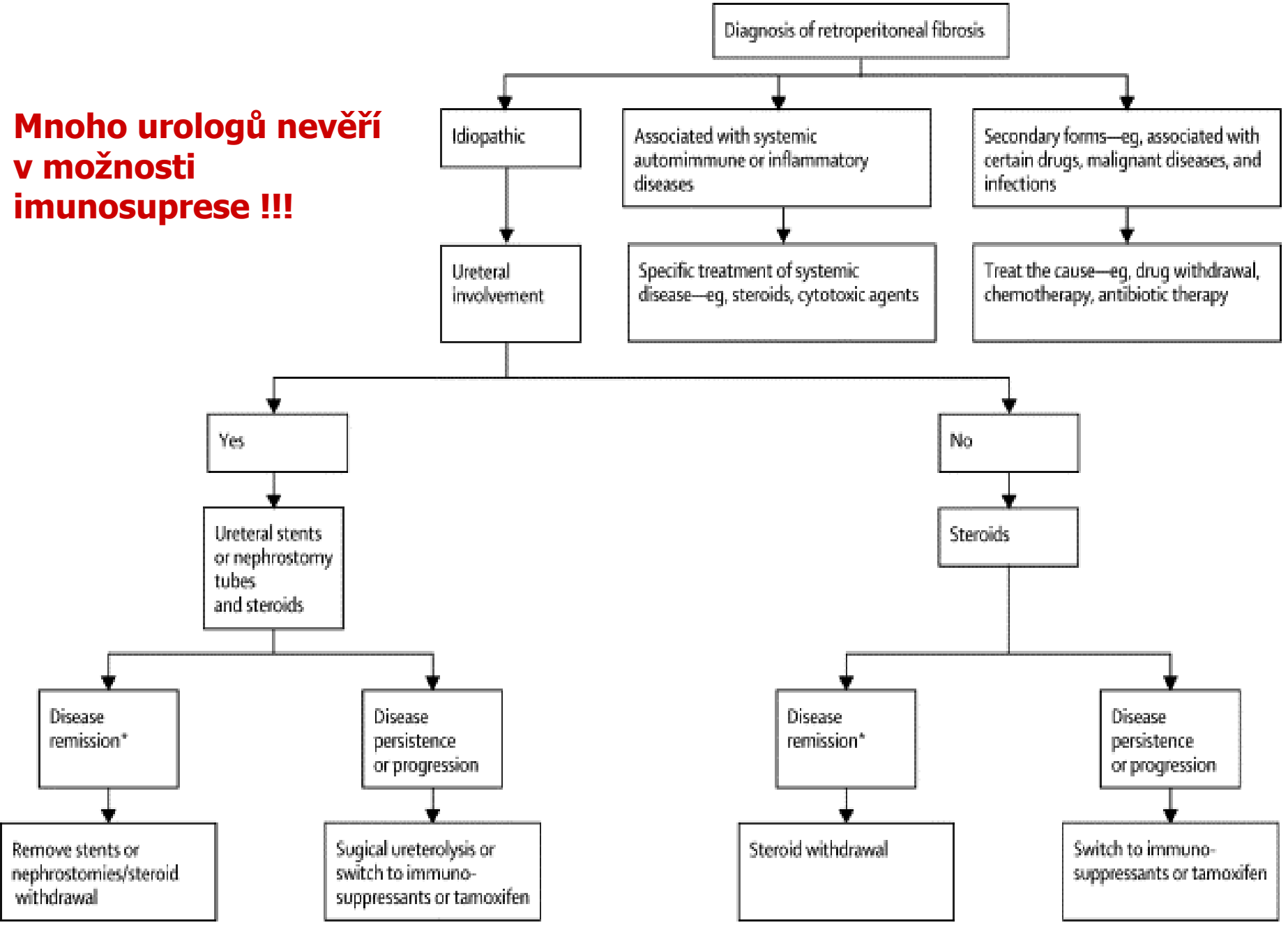
TABLE 3
Radiographic Classification at Initial Visit for 28 Patients With RPF

Radiographic Class *	No. (%)
I	4 (13)
I + II	5 (16)
I + III	2 (6)
I,II,III	10 (32)
I,II,IV	1 (3)
I,II,III,IV	9 (29)

* Class I: Soft-tissue density surrounding the infrarenal aorta and /or iliac vessels; Class II: Soft-tissue density surrounding the infrarenal vena cava; Class III: Lateral extension of the inflammation/fibrosis with compression of one or both ureters; Class IV: Extension of inflammation/fibrosis to include the renal hilum with compression of the renal artery and/or renal vein.

I fibróza kolem infrarenální aorty a/nebo iliakálních tepen
II fibróza kolem infrarenální v.cava
III laterální expanze fibrózy s kompresí jednoho nebo obou ureterů 1
IV expanze fibrózy s postižením ledvinného hilu a kompresí renální arterie a/nebo žíly

Mnoho urologů nevěří v možnosti imunosuprese !!!



NNH Ormondova choroba

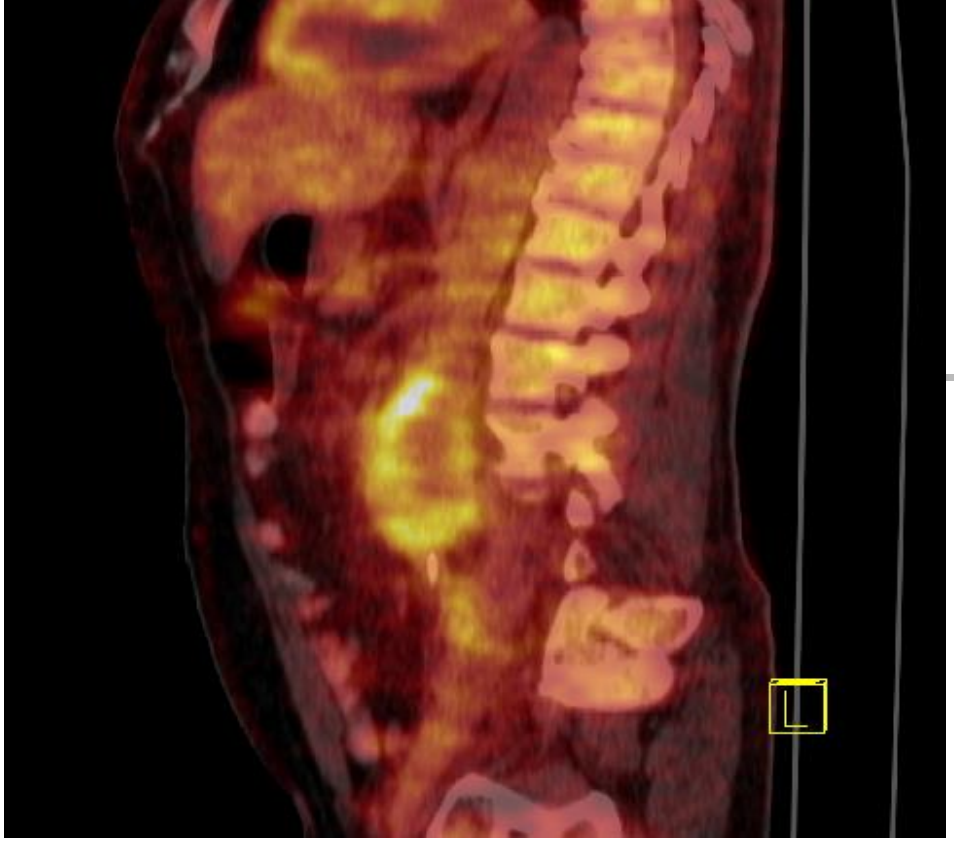
- **28 pacientů s Mb.Ormond – klasické postižení retroperitonea, ledvin a močovodů**
- **Ve všech případech nasazena imunosuprese pro aktivitu onemocnění, s verifikací PET/CT a ukončením léčby - verifikováno PET/CT**
- **Recidiva nebyla zaznamenána**
- **Ve 2 případech „záchrana „ ledviny**
- **U 15 pacientů definitivní odstranění stentů**

Ormondova choroba s postižením cév

- **13 pacientů**
- **Periaortitida, aortitida s postižením břišní popř. hrudní aorty**
- **Aktivita onemocnění – ve 3 případech terapie nenasazena a remise trvá**
- **1x recidiva – špatná compliance pacienta**
- **Verifikace – PET/CT**
- **U 6 pacientů byl proveden operační výkon**

Kazuistika

- **Muž 54 let**
- **Thajsko, 3 týdny poté febrilie, únava…**
- **Při progresi vyšetřen na interní klinice s nálezem perakutního selhání ledvin a aneurysmatem aorty**
- **Při CT podezření na Mb. Ormond… vyšetřovací standardní schéma s důrazem na rychlost, ale..**
- **Pozitivní quantiferonový test , PET/CT suspekce…..**
- **Provedena při laparoskopii biopsie s vyšetřením tkáně na TBC pomocí PCR**
- **Nasazena imunosupresivní terapie s pokrytím potencionální TBC**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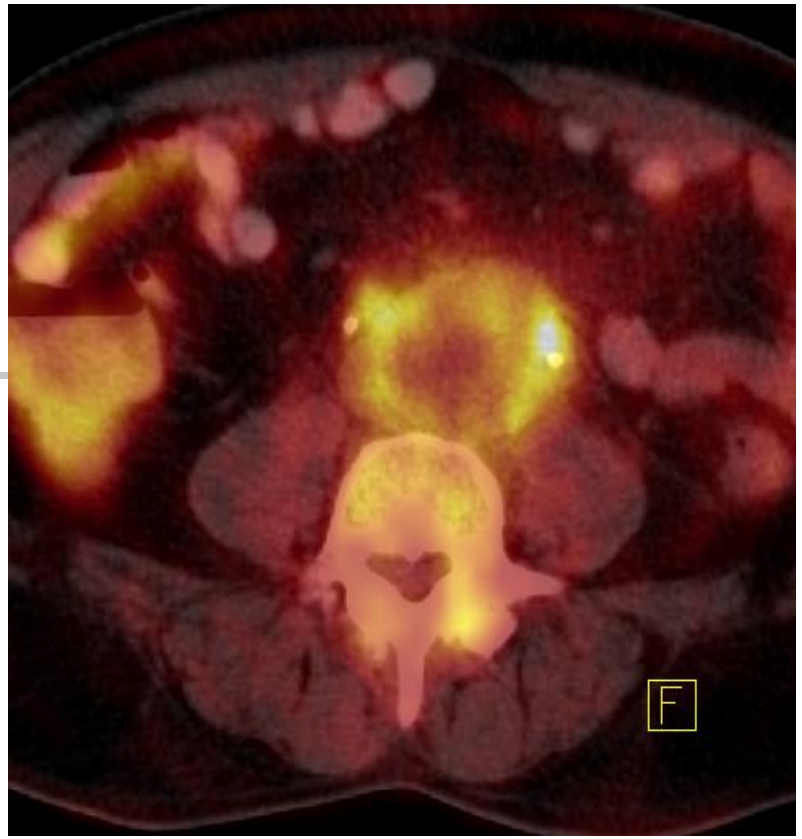
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Kazuistika

- **Špatná compliance pacienta**
- **Urgentní příjem na oddělení cévní chirurgie**
- **Komplikovaná operace s reoperací a finálním řešením pomocí stentu**
- **Vznik abscesu periaortálně s nemožností chirurgického řešení, vznik discitidy**
- **Dlouhodobá parenterální ATB terapie s potencionálem intervence cévních chirurgů**

Problémy - otázky

- **Diagnostické – neexistuje specifický marker**
- **Dif. dg infekční vs. neinfekční zánět**
- **Proč u některých pacientů není „aktivita“ zánětu? a je to skutečně pravda? (nové biomarkery)**
- **Terapeutické**
- **Jak postupovat u recidivy špatně reagující na „klasickou“ imunosupresi?**
- **MFM, biologická terapie**

SOUHRN

- **Ormondova choroba onemocnění mnoha tváří**
- **Při periaortitidě je extrémně důležité rozlišení infekční a neinfekční etiologie**
- **Imunosupresivní léčba je lékem volby společně s urologickým a/nebo ošetřením cévním chirurgem**

Table 1. Pathways and Processes in Fibrogenesis and Current Treatments.*

Organ	Pathways and Processes	Diseases	Drugs	Summary of Effectiveness	Source of Data†
Heart	Aldosterone antagonism, TGF-β antagonism, RAS inhibition, cGMP inhibition, inhibition of cholesterol synthesis, inhibition of Na-K-Cl cotransporter	Heart failure, cardiomyopathy, hypertrophic cardiomyopathy, cardiomyopathy induced by type 2 diabetes, heart failure or cardiomyopathy induced by hypertension	Spironolactone, eplerenone, canrenone, pirfenidone, sildenafil, statins, ACE inhibitors, ARBs, torsemide, MRAs	ACE inhibitors, ARBs, and MRAs are associated with decreased fibrosis on MRI and decreased arrhythmogenesis (the latter suggests effects of drugs on fibrosis)	Kosmala et al.,[67] Giannetta et al.,[68] Antonopoulos et al.,[69] Roubille et al.,[70] TORAFIC Investigators Group[71]
Liver	RAS inhibition, inhibition of collagen synthesis, inhibition of effector-cell fibrogenesis, inhibition of oxidative stress, signaling of PPAR γ-agonists	Many diseases of the liver	ACE inhibitors, ARBs, colchicine, interferon γ-1b, vitamin E, pioglitazone, farglitazar	Specific antifibrotic agents listed have generally been ineffective in halting or reversing fibrosis	Sanyal et al.,[72] Kim et al.,[73] Kershenobich et al.,[74] Morgan et al.,[75] Muir et al.,[76] Pockros et al.,[77] McHutchison et al.[78]
Kidney	RAS inhibition, aldosterone antagonism, TGF-β antagonism, Nrf2 pathway	Primarily renal diseases related to hypertension or diabetes	ACE inhibitors, ARBs, spironolactone, pirfenidone, bardoxolone	ACE inhibitors and ARBs are moderately effective in slowing progression of diabetic nephropathy (indirectly suggesting effects on fibrosis)	Lambers Heerspink et al.,[79] Ruggenenti et al.,[80] Bonventre,[81] Guney et al.,[82] Sharma et al.,[83] de Zeeuw et al.[84]
Lung	TGF-β antagonism, direct inhibition of effector-cell fibrogenesis, multikinase inhibition, inhibition of oxidative stress	Primarily idiopathic pulmonary fibrosis	Pirfenidone, interferon γ-1b, bosentan, ambrisentan, macitentan, nintedanib, acetylcysteine	Pirfenidone and nintedanib led to improvements in clinical outcomes	Raghu et al.,[85-87] King et al.,[88] Richeldi et al.,[89] Martinez et al.[90]
Skin	Endothelin-receptor antagonism, multikinase inhibition	Scleroderma, nephrogenic systemic fibrosis	Bosentan, imatinib mesylate	Small studies show modest effects	Kuhn et al.,[91] Kay and High[92]

* ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, cGMP cyclic guanosine monophosphate, MRA mineralocorticoid-receptor antagonist, MRI magnetic resonance imaging, Nrf2 nuclear factor erythroid 2–related factor, PPAR peroxisome proliferator-activated receptor, RAS renin–angiotensin system, and TGF-β transforming growth factor beta.

† Detailed information about specific trials is provided in Table S1 in the Supplementary Appendix.