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THURSDAY, 13 JUNE 2019

15:30:00 – 17:00:00

Interstitial lung disease in rheumatic diseases and systemic sclerosis

SP0071 WIN: SYSTEMIC SCLEROSIS – INNOVATIVE TREATMENT TARGETS OR “LOST IN TRANSLATION”?

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Interstitial lung diseases (ILDs) are a group of heterogeneous disorders, either idiopathic (idiopathic pulmonary fibrosis-IPF) or associated with other diseases, particularly autoimmune diseases, from which systemic sclerosis is the leading disease at risk of developing ILD. It has been proposed that for clinical research and patient management various subsets of fibrosing ILD that have similar biological and clinical behaviours could be merged into a single entity although specificities within each disease remain, with various patterns of lung injury. Nevertheless, the shared part relates to progressive fibrosing ILD leading to progressive decline in lung function and early mortality. In SSC, a recent report from EUSTAR network showed that ILD was nowadays the first cause of death identified as contributing to 17% of deaths (1).

No drugs are licensed for the treatment of ILDs related to autoimmune diseases. Treatment guidelines issued by the European League Against Rheumatism (EULAR) recommend tailored therapy with cyclophosphamide (CYC) for SSC-ILD, in particular for patients with progressive ILD (2). Indeed, 3 randomized controlled trials showed some benefits of using CYC either orally or by infusion route although the effect size was small and the clinical translation of the findings was difficult to establish. The limitations of CYC trials in SSC-ILD led the experts to add that dose and duration of treatment need to be tailored individually dependent on the clinical condition and response. Furthermore, with regards to safety, potential risks of bone marrow suppression, teratogenicity, gonadal failure and haemorrhagic cystitis must be always considered. Beyond standard immunosuppression, the use of high dose CYC, with or without irradiation, but using rescue with stem cells showed some effects on ILD measured through lung function and imaging. Nevertheless, considering the risk of potential treatment-related mortality and morbidity, the EULAR experts recommend that HSCT should be considered for the treatment of selected patients with rapidly progressive SSC at risk of organ failure, two domains which remain to be delineated. Altogether these results suggest that immunosuppressants might be beneficial in the context of SSC-ILD although the right drug, the right dosing and the right patients still need to be defined. In practice, because of SLS2 trial, mycophenolate mofetil has emerged as the leading drug used when a physician aims at treating SSC-ILD. The understanding of SSC and SSC-ILD have improved in the recent years and subset at risk and candidate biomarkers have emerged. Indeed, interleukin 6 has been shown to predict some disease progression including lung involvement. Therefore, targeted therapy against IL6 is an appealing strategy to improve SSC outcomes. If the pivotal trials using tocilizumab had skin as a primary outcome and failed to meet the primary end-point, secondary analyses revealed stimulating lung results that will be showed during EULAR 2019 and discussed within the ILD session. B-cells role has also been scrutinized in SSC with promising data. Therefore, rituximab is used in some SSC patients with various indications according to physician views and experience. EUSTAR has assembled a large group of rituximab treated patients and performed a well-designed observational study that did not show clear evidence supporting some efficacy of rituximab on SSC-ILD although some clues emerged.

The role of antifibrotic drugs (nintedanib, pirfenidone), that showed to slow disease progression in patients with IPF, in patients in other forms of fibrosing ILD remains to be determined. However, several trials are ongoing and the results of

the SENSICIS trial evaluating nintedanib in SSC-ILD will be presented during EULAR 2019 and discussed during the ILD session.

Altogether, the available results show some progresses made in the management of SSC-ILD, so far mainly through the use of treatment targeting immune disturbances. Considering the severity and the complexity of SSC pathogenesis and related lung complication, one might anticipate that if trials of antifibrotic therapies are positive, the treatment of SSC-ILD, and maybe of all fibrosing autoimmune ILDs, might involve combination of immunosuppression and antifibrotic therapies.

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THURSDAY, 13 JUNE 2019

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Diagnostic challenges in vasculitis

SP0072 IMAGING IN THE DIAGNOSIS OF LARGE VESSEL VASCULITIS

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Background: Giant cell arteritis (GCA) and Takayasu arteritis (TAK) are large-vessel vasculitides (LVV). Recommendations demanded so far to confirm the diagnosis histologically, particularly in suspected GCA. Biopsy is however invasive, and results are not immediately available. Technology has rapidly improved; and many recent studies suggest that imaging may have comparable diagnostic accuracy.

Objectives: To provide an overview of new developments for ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and 18-fluorodeoxyglucose positron emission tomography (PET) in diagnosis of LVV and to present new EULAR recommendations on imaging in LVV.

Methods: A systematic literature review and meta-analysis of diagnostic and prognostic studies enrolling >20 patients and investigating ultrasound, MRI, CT or PET in patients with suspected and/or established primary LVV was conducted (1). On this basis, a group of imaging experts, rheumatologists, patients and health care professionals developed EULAR recommendations on imaging in LVV (2). This review refers also to new data after the EULAR recommendations had been published.

Results: In suspected GCA, imaging should be done early, but without delaying treatment. No further diagnostic test (histology or other imaging) is necessary if results of imaging and clinical presentation correspond. Ultrasound of temporal and axillary artery arteries showing a non-compressible ‘halo-sign’ is the method of first choice in suspected cranial GCA. The meta-analysis showed positive and negative likelihood ratios of 19 and 0.2, respectively, for a final diagnosis of GCA. Good data is also available on MRI of cranial arteries. Ultrasound, MRI, CT or PET can be applied for confirming extracranial GCA. Ultrasound is of limited value for assessing particularly the thoracic aorta. MRI is first choice for suspected Takayasu arteritis, but ultrasound, CT or PET can be also applied. Conventional angiography is not recommended instead for interventions. Imaging might be useful in suspected flare and to monitor damage. There is no convincing evidence to recommend routine monitoring in remission. Imaging should be done by a trained specialist using appropriate equipment.

Particularly ultrasound of cranial arteries showed high diagnostic accuracy in a study for developing new classification criteria. Measuring intima thickness (cut-offs of around 0.4 mm for temporal and 1.0 mm for axillary arteries) may help to improve diagnostic accuracy and to use ultrasound for disease monitoring in trials (3). Reliabilities of sonographers both for evaluating videos and for examining patients directly were very high (4,5). Newer PET technology now allows to also show inflamed temporal, maxillary and vertebral arteries (6). The significance of positive imaging findings in follow-up studies still remains unclear. The incidence of vision loss decreased with the introduction of fast-track clinics. These clinics are increasingly established in centres. They include referral within one working day to a rheumatologist followed by immediate imaging for establishing the diagnosis. Imaging can be done by the rheumatologist (most commonly ultrasound) or by a collaborating department.

Conclusion: Ultrasound, MRI, CT and PET allow to confirm or exclude LVV provided that it is performed by a trained specialist using appropriate equipment. Fast-track clinics using ultrasound are increasingly established in rheumatology.

Ultrasound showed high diagnostic accuracy. Modern PET equipment may also delineate vasculitic temporal, maxillary and vertebral arteries. The significance of follow-up imaging studies in LVV still needs to be determined.

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SP0073 DIAGNOSIS OF GASTROINTESTINAL VASCULITIS

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The gastrointestinal vasculature can be involved by a variety of vasculitis affecting large, medium, small or variable vessel size according to the 2012 revised Chapel Hill consensus nomenclature. Gastrointestinal involvement (GI) is one of the most severe complications of vasculitis requiring intensive immunosuppressive therapy and sometimes revascularization techniques or emergency surgery and may affect a variety of organs including large or small intestines, liver, biliary tract, pancreas, and less frequently, stomach or oesophagus. It can complicate the course of patient with known or with overt suspicion of vasculitis or be the main or even the only manifestation of these diseases.

Clinical manifestations range from abdominal pain, sometimes colicky, that usually worsens after eating to overt signs of bowel ischaemia or perforation with diffuse and constant abdominal pain, reduced peristalsis, abdominal defence and distension, and signs of peritoneal irritation. GI bleeding, frequently in the form of occult blood loss or haematochezia and less frequently melena or rectorrhagia, is common. Non-specific symptoms such as nausea, vomiting or diarrhoea may be observed. Pancreatitis, cholecystitis or appendicitis may also occur.

In large-vessel vasculitis, including giant-cell arteritis (GCA) and Takayasu disease (TAK), inflammation usually affects the proximal portion of the celiac trunk, hepatic or mesenteric arteries. GI involvement is rare in GCA with only isolated cases or small series having been reported. About 30% of patients with GCA have elevated hepatic enzymes as part of the acute phase response and rarely reflect involvement of the hepatic vasculature. Imaging techniques disclose stenotic or occlusive lesions in 25% of patients with TAK but clinically manifest involvement occur in about 16% of patients. Abdominal pain suggestive of vascular insufficiency is present in about 16% of patients; abdominal bruits can be perceived in 14% but only 4% present with overt signs of mesenteric ischemia. Due to the involvement of the proximal part of the GI branches, the ischemic territories may be extensive but usually progression of vascular occlusion is not abrupt, and due to the size of vessels involved, patients may benefit from percutaneous revascularization procedures if immunosuppressive treatments are not sufficient. Interestingly 5% of patients with TAK also suffer from inflammatory bowel disease, particularly Crohn's disease.

In medium sized vasculitis, such as polyarteritis nodosa (PAN) or Kawasaki disease (KD), multiple muscular artery branches of the GI vasculature can be involved. Abdominal pain is frequent in PAN (35-95% of cases). GI involvement is more frequent in HBV-associated PAN than in idiopathic PAN. About 61% of patient with KD may have GI symptoms but these are severe in 4.6% only. Gallbladder hydrops and appendicular vasculitis may occur. The presence of prominent GI manifestations is more frequent in patients with coronary aneurysms indicating more severe vasculitic disease.

In small-vessel vasculitis, including anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)(granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA], and eosinophilic granulomatosis with polyangiitis [EGPA]) and immune-complex-mediated vasculitis (IgA vasculitis [Henoch-Shönlein purpura] and cryoglobulinemic vasculitis) the microvasculature is segmentally affected and the severity of involvement may be variable in different areas. Among AAV, GI involvement is more frequent in patients with EGPA (35-50%), than MPA (5-30%) or GPA (5-11%). In EGPA, GI involvement can be vascular as in other vasculitis or may be in the form of eosinophilic gastroenteritis or esophagitis. In GPA, in addition to vascular involvement, granulomatous hepatitis or pancreatitis may occasionally occur. Among immune-complex vasculitis, GI involvement is typical in IgA vasculitis, occurring in 50-75% of patients. Although it is usually mild and

self-limited, complications including bleeding, ischaemia, perforation or intussusception may appear in 3-5% of patients. Hepatobiliary involvement is uncommon (1.8%). GI involvement is rare in cryoglobulinemic vasculitis but is life-threatening when it occurs.

Among the category of variable vessel size vasculitis, GI involvement in Behçet's disease (BD) may consist of mucosal ulcers, frequently in the distal ileum, similar to inflammatory bowel disease, or involvement of mesenteric artery branches as in other vasculitis. Venous thrombosis involving the liver vasculature or GI tract may also occur in BD.

Vasculitis involvement may be restricted to different portions of the GI tract (gallbladder, appendix, intestines) in patients with no obvious evidence of systemic vasculitis. Gallbladder is the more frequent location and is usually incidentally discovered after surgery. Overt systemic vasculitis may develop in up to 25% of patients during follow-up.

Diagnosis of GI involvement in systemic vasculitis requires clinical suspicion. Imaging (computed tomography [CT]-angiography[CTA] or magnetic resonance angiography [MRA] are crucial in large vessel vasculitis evidencing concentric thickening with contrast enhancement of the vessel wall, along with lumen reduction. In medium vessel vasculitis CT may disclose hepatic, spleen or renal infarcts that reinforce clinical suspicion of vascular disease. However, CTA or MRA may not have enough resolution to evidence involvement of medium-sized branches and conventional angiography is usually needed, revealing vascular stenosis or occlusions as well as microaneurysms. In small-vessel vasculitis, and in all vasculitis conveying intestinal ischemia, CT may reveal thickening of the intestine wall, dilatation, and, in severe cases, pneumatosis of the intestine wall as well as gas in the portal system. Pneumo-peritoneum can be seen in the case of perforation. Ascites is not uncommon in medium and small vessel vasculitis. Occasionally, hemorrhage in the peritoneal cavity due to rupture of aneurysms can be observed. It is important to remark that imaging findings provide strong support to the clinical suspicion of vasculitis based on additional clinical, blood test or serologic findings or evidence of vasculitis elsewhere but similar findings can be observed in the context of a variety of vasculopathies or thrombophilic/embolic disorders that may mimic vasculitis.

Endoscopy is also a useful exploration in some settings. It may detect intestinal purpura, usually in IgA vasculitis, mucosal ulcers or mucosal inflammation. Endoscopic biopsies may reveal eosinophilic inflammation in EGPA but may not be deep enough to disclose inflamed blood vessels and its absence does not exclude vasculitis. In case of surgical complications, a throughout pathologic examination of the removed specimen should be requested in order to evidence of vascular inflammation.

GI involvement in systemic vasculitis is frequently a severe and potentially life-threatening complication. Prompt detection and intense immunosuppressive, revascularization or surgical treatment in the appropriate settings are crucial for a successful recovery and prevention of irreversible damage.

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