OP17. PATHOLOGIC FEATURES OF TAKAYASU’S ARTERITIS (NON SPECIFIC AORTOARTERITIS)

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Takayasu’s arteritis or Non-specific aortoarteritis (NSAA) is an uncommon form of large vessel vasculitis and has been known by various names.

The morbid anatomical features of NSAA described here are based on the autopsy findings of 80 cases seen in a 30-year period. These autopsies were carried out at Seth GS Medical College & KEM hospital, Mumbai. With an active autopsy service, the incidence of NSAA is about 0.15%. 46.25% of these cases were in the pediatric age group.

In the aorta the disease had 2 patterns of involvement: (a) Segmental lesions either single or multiple, with skip areas in between. (b) Diffuse extensive disease. Marked periadventitial and adventitial fibrous thickening with adhesions to neighboring structures with enlarged lymph nodes is often noted around the involved segments. The aorta is stiff and rigid, sometimes with dilated segments and aneurysms.

Localised stenotic lesions is fairly common (37.5%), seen particularly in children and is noted in the descending thoracic (DTA) and abdominal aorta. In our material the DTA is the segment maximally affected. The lesion starts at the level of L subclavian or just beyond it to involve variable lengths of DTA. Abdominal aorta (renal artery segment) disease is more common in adults. This is often associated with renal artery stenosis. In diffuse disease the thoracic abdominal aorta is affected, sparing the ascending aorta. In autopsy material, isolated arch vessel disease is rare. When arch vessel is diseased, it involves mainly the L Subclavian and there is always associated aortic arch disease. Arch vessel disease is in the form of complete block or osteal narrowing with occlusive luminal thrombi. Coronary ostial stenosis is not uncommon.

The intimal surface of the aorta is covered with gelatinous or whithish plaques or is diffusely thickened. Mural thrombi are sometimes present in the constricted segment.

Histopathological features: Inflammation may be in the active or more commonly in the chronic healed phase. In the active phase, diffuse or granulomatous inflammation is seen consisting of Langhans giant cells, foreign body giant cells, mixed inflammatory cells and sometimes-fibroid necrosis. Inflammatory reaction is maximal at the junction of the media and adventitia and is marked around vasas vorum though there is no vasculitis. Adventitia shows increase in ground substance with acid mucopolysaccharides. Media shows neovascularization and inflammatory cells. Intima is thickened with increase in ground substance. There is no intimitis. In chronic phase there is sparse inflammation around vasas vorum, adventitial thickening, fibrosis, scarring in the media, disruption of elastic fibres and hyaline intimal thickening. Pulmonary artery and coronary artery involvement is infrequent.

The commonest associated pathology noted at autopsy is tuberculous lymphadenitis (55%). Matted enlarged Para aortic and mediastinal lymph nodes are particularly present around the involved segments of aorta.

It is not easy to reconstruct the natural course of the disease. Symptoms are related to well establish lesions in the aorta or its branches. The inflammatory process may be self limiting in most cases. Regression of lesions has been documented in a few case reports. Prognosis is influenced by clinical course, age of onset and complications like hypertension, rapid development of congestive cardiac failure, and left ventricular failure.

As of today there is no specific disease activity marker and treatment should be aimed at preventing vital organ ischemia and cardiac failure.

OP18. FACTORS INVOLVED IN THE PERSISTENCE OF INFLAMMATORY LESIONS IN GIANT CELL ARTERITIS (GCA)

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Patients with GCA usually experience a dramatic relief of their cranial, polymyalgic and systemic symptoms with corticosteroid treatment. However, recurrences are frequent during steroid tapering and corticosteroid requirements are highly variable among individuals: while some patients easily enter sustained remission, others require remarkable cumulated corticosteroid doses with their ensuing adverse effects.

We and others have empirically observed that the intensity of the acute phase response is associated with different disease outcomes. Patients with a weak acute phase response have higher risk of developing disease-related ischemic events. These patients have weaker expression of pro-inflammatory cytokines in their lesions, lower concentrations of pro-inflammatory cytokines in their sera, weaker angiogenic response in their lesions, and lower expression of endothelial cell adhesion molecules. These patients achieve more rapidly a sustained remission, suffer from fewer relapses, and require lower cumulated corticosteroid doses. At the opposite edge of the spectrum, patients with a strong systemic inflammatory response have higher tissue production and circulating levels of pro-inflammatory cytokines, and prominent neovascularization in their lesions with strong expression of endothelial cell adhesion molecules. Although these patients have lower frequency of ischemic events, they suffer from a more refractory disease. These observations support the concept that, in some patients, GCA would easily evolve to a healing stage with higher risk of ischemic complications, perhaps facilitated by the scarring process itself, whereas other patients would develop a perpetuating disease with sustained inflammatory cascades with vascular regeneration and remodelling, leading to a more refractory and relapsing outcome.

Proinflammatory cytokines IL-1β, TNFα and IL-6 may have an important role in contributing to these different outcomes. Their tissue expression correlates with the intensity of the acute phase reaction. In addition, TNFα, and, IL-1β, mRNA concentrations in lesions correlate with subsequent corticosteroid requirements. Based on their known biologic functions, pro-inflammatory cytokines may have important roles in perpetuating the inflammatory process by amplifying inflammatory cascades such as endothelial adhesion molecule expression, chemokine and cytokine production and by triggering the acute phase response leading to the general feeling of sickness in patients with GCA. Alternatively, these cytokines may be the downstream products of more relevant factors or may be co-ordinately regulated with other molecules with a more direct impact on the course of GCA.

Comparison of gene expression in vascular inflammatory lesions between easy responders and refractory patients may help to identify additional factors involved in persistence of inflammation in GCA. Using this approach we have identified CCL-2 (MCP-1) a powerful chemotactic factor for monocytes and Th1 lymphocytes, as a significant molecule associated with disease refractoriness.

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OP19. ENDOTHELIAL CELL PATHOBIOLOGY
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Associations exist between acute and chronic inflammatory exposures and cardiovascular events. Acute infection or surgery are associated with a transient increase in the risk of stroke and myocardial infarction, and a number of autoimmune and chronic inflammatory disorders are associated with an increase in such risk over the longer term, though a causal link has yet to be proven in humans. Products of the inflammatory response have effects on the vascular endothelium that might attenuate its normal atheroprotective functions, and could provide a mechanistic link between inflammation and cardiovascular disease. Whether interventions to modify the inflammatory response would be efficacious in reducing cardiovascular events in acute or chronic settings is yet uncertain.

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OP20. IMAGING ENDOTHELIAL ACTIVATION IN INFLAMMATION
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Despite the important role that endothelial activation plays during inflammatory responses, molecular changes in endothelium are relatively inaccessible to clinical investigation. E-selectin (CD62E, ELAM-1) is an adhesion molecule expressed on the luminal surface of vascular endothelial cells in inflammation. It serves the function of initiating interactions between the endothelial cell and circulating leucocytes, preceding leucocyte diapedesis into inflamed tissue. E-selectin is not constitutively expressed by endothelial cells but is induced in response to cytokines during many inflammatory conditions, including sepsis, inflammatory bowel disease, atherosclerosis, and rheumatoid arthritis. E-selectin represents a potentially useful target for the molecular imaging of endothelial activation, since it is readily accessible to targeting agents. Furthermore, following expression, E-selectin is internalised, and agents conjugated to anti-E-selectin antibodies are taken with E-selectin into the cell, allowing accumulation of targeting agent and increased imaging signal. Monoclonal antibody 1.2B6 is a mouse antibody generated in our laboratory, which primarily reacts with E-selectin but also reacts with 111In-labelled mAb 1.2B6 (F(ab')2 were significantly more focal and intense than those obtained with an isotype matched control mAb or 99mTc-labelled leucocytes. We have since shown that 111In-labelled mAb 1.2B6 (F(ab')2 could image inflamed joints in patients with RA [1–3] and inflamed bowel in Crohn’s Disease and Ulcerative Colitis [4]. More recently we have investigated the possibility of imaging E-selectin by magnetic resonance imaging using anti-E-selectin conjugated ultrasmall superparamagnetic iron oxide nanoparticles.

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OP21. ULTRASOUND IN GIANT CELL ARTERITIS
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Background: Several imaging studies have been recently applied in diagnosis of GCA. They display characteristic wall swelling, stenoses, and occlusions of arteries. Since resolution of ultrasound is as high as 0.1 mm, it detects characteristic pathologies not only in axillary and subclavian arteries but also in temporal and other rather small arteries.

Methods: A meta-analysis evaluated 23 studies on temporal artery ultrasound. The author has personally investigated >1000 subjects including >150 patients with active GCA, >25 of whom had large-vessel GCA. Colour Doppler ultrasound evaluates wall swelling. Duplex ultrasound additionally investigates blood flow characteristics for stenoses and occlusions.

Results: The meta-analysis describes a sensitivity of 87% and a specificity of 96% for duplex ultrasound with regard to clinical diagnosis. Sensitivity is similar in our cohort, but specificity is >99%. Results are varying considerably between studies. Specificities with regard to histology vary between 40% and 100% for colour Doppler and between 91% and 100% for duplex ultrasound. Specificities vary between 68% and 100% for histology and between 78% and 100% for the clinical diagnosis.

Conclusion: Duplex ultrasound of the temporal arteries but also of most of the other arteries is now widely used in diagnosis of GCA. It is a precise imaging study if an experienced sonographer uses good equipment with correct machine adjustments, and considers wall swelling, stenosis, and occlusions.