ORAL PRESENTATIONS

OP1. HISTORY OF GIANT CELL ARTERITIS (GCA) AND POLYMYALGIA RHEUMATICA (PMR)
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Whether GCA and PMR existed in antiquity, or are conditions of modern times is unknown. Hutchinson’s report in 1890 of an elderly man with “red streaks” on his forehead appears to be the first detailed case. In 1930, Schmidt discussed a patient with symptoms of GCA but attributed them to aneurysm. In 1932, Horton et al. reported 2 patients whose temporal artery biopsies showed arteritis. In 1937, these workers summarized 7 cases who manifested systemic symptoms, headache, fever, anemia and jaw claudication. Temporal artery biopsies showed granulomatous inflammation with giant cells. The authors considered this a new vasculitis calling it “temporal arteritis”.

Over the next decade occasional cases were published describing many of the symptoms of GCA. In 1938, Jennings observed a patient with visual loss. In the 1941, Gilmour reported autopsy findings in 3 older patients with inflammation in large vessels that appeared similar to temporal arteritis. He suggested the name “giant cell arteritis”. In 1946, Kilbourne and Wolff, noted involvement of multiple cranial vessels and offered the name “cranial arteritis”.

PMR was also described in the late 19th century, by Bruce in 1888. Some physicians (e.g. Copeman, Slocumb, Hamrin) stated that PMR was recognized as a clinical syndrome in the 1930’s or even before, although not written about. However, it wasn’t until the 1940’s and early 1950’s that reports on this condition started to appear under a variety of names such as secondary fibrositis, periarteritis nodosa, rheumatism, myalgic syndrome of the aged, pseudo-polymyalgia rhizomelique, and anarthritic rheumatoid disease. Barber’s article in 1957 in which he coined the term “polymyalgia rheumatica” caught the attention of many, and this name was eventually adopted. In the 1950s, shortly after the discovery of the potent anti-inflammatory properties of cortisone, Birkhead and colleagues showed that GCA responded well to this drug. Later, low doses were found also to be very effective in PMR.

The link between GCA and PMR wasn’t recognized immediately. But, in the 1940’s and 1950’s, several authors noted that some patients with GCA had findings of PMR. The reports by Paulley and Hughes, Alestig and Barr, Hamrin, and others in the 1960’s, led to a wider appreciation of a close connection between PMR and GCA. Modern research on these conditions has increased our understanding substantially. However, much more knowledge is needed and only waits to be discovered by the skilled, inquiring, and dedicated scientist.

OP2. PATHOGENESIS OF GCA AND PMR
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As artery size increases, a sophisticated wall structure is required to support critical function in oxygen and nutrient transport. Blood supply to the arterial wall itself is provided from the most peripheral layer, the adventitia, which holds a dense system of vasa vasorum. Recent evidence suggests that the adventitia makes additional contributions to securing blood vessel function and health. Specifically, the adventitia is home to an indigenous population of dendritic cells (DCs) that are arranged circumferentially at the adventitia-media border and play an important role in regulating the immunogenicity of the artery.

DCs are powerful antigen-presenting cells that can prime naïve T cells. In order to investigate the function of tissue-residing DCs placed in the adventitia, we implanted medium-sized human arteries into SCID mice and adoptively transferred alloreactive T cells. Adventitial DCs avoided recognition by alloreactive T cells, suggesting that they may have a role in protecting the tissue site from inflammation. Systemic administration of Toll-like receptor ligands, especially ligands specific for TLR2 and TLR4, was sufficient to transform non-stimulatory DCs into highly activated effector cells. Triggered by TLR4 ligands, adventitial DCs released chemokines, attracted T cells, facilitated T-cell stimulation and supported invasion of T cells into the media. We conclude that immune recognition events in the vascular wall are principally regulated through indigenous DCs that are placed at the outskirts of the artery.

In patients with giant cell arteritis (GCA), a granulomatous vasculitis of medium-sized and large arteries, dense networks of DCs occupy the adventitia and media. In vasculitic lesions, DCs produce CXCL19 and CCL21, and trap themselves through the expression of CCR7. Activation of CD4 T cells continuously depends upon DC-derived signals as demonstrated by the strong immunosuppressive effects achieved through depletion of activated DCs. DC depletion essentially destroyed the sophisticated organization of the T cell-macrophage infiltrates and disrupted production of the key cytokine IFN-γ. In patients with polymyalgia rheumatica (PMR), a forme fruste of GCA lacking vascular infiltrates, the vessel wall DCs are already activated and capable of promoting T-cell stimulation. These data support the model that DCs strategically placed in the adventitia control tissue inflammation in the unique microenvironment of the vessel wall structure and make critical contributions to initiating and maintaining vasculitis.

OP3. IMMUNOGENETICS OF GCA AND PMR
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Giant cell (temporal) arteritis (GCA) and polymyalgia rheumatica (PMR) are different but overlapping diseases. GCA is a common vasculitic syndrome in Western countries that involves the large and middle sized blood vessels with predisposition to the cranial arteries in the elderly. PMR is also a common condition of the elderly with symptoms of pain and morning stiffness involving the neck, shoulder and hip girdle, which are generally associated with a raised ESR. PMR is observed in up to 50% of patients with GCA.

The aetiology of these conditions remain unknown but are likely to represent dysregulation of an ageing immune system in genetically susceptible individuals. Both conditions represent complex clinical phenotypes and are likely to be due to the interactions of multiple genetic factors and environmental triggers.

Both GCA and PMR have been associated with HLA and other immunoregulatory candidate genes largely using case-control association studies. These have indicated that some genetic associations are restricted to GCA and others to just PMR. In contrast, some associations appear to be common to both. These may explain the overlap of phenotype in some patients.

To date, the selection of which candidate genes to test has come from what is known about the regulation of immune response and macrophage activation (cytokines, adhesion molecules,