# The bias in the nomenclature of large vessel vasculitis

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## Key Message

A 68-year-old man presenting with the phenotype of 'pulseless disease' leads us to challenge current differentiation of Takayasu arteritis and GCA.

Dear Editor,

A 68-year-old man of Northern European ancestry presented with a 3-month history of constitutional symptoms to his general practitioner. The detection of a normochromic normocytic anaemia, an acute phase response and an elevated prostate specific antigen prompted a referral to a rapid diagnostic service for cancer. A CT-scan of the thorax, abdomen and pelvis did not detect any solid tumours but commented on thickened aorta. An urgent referral was made to the vasculitis clinic. In the interim he received a short course of prednisolone which had finished more than a week ago.

On attendance in vasculitis clinic, he had no organ-specific symptoms. Constitutional symptoms included weight loss of >5kg, drenching night sweats, and fatigue. He reported feeling slightly better over the last few weeks. He did not have any risk factors for atherosclerosis. On direct questioning, he admitted to a mild frontal headache (which had been reported as being absent in the primary care referral letter), anterior neck pain, and symmetrical shoulder pain. On examination, there were no nail changes or detectable lymphadenopathy. The radial pulses and blood pressure were difficult to elicit in both arms, but the extremities appeared well perfused. There were harsh bruits over both subclavian and axillary arteries. Carotid arteries did not exhibit bruits and were non-tender. There were no abnormalities in relation to the superficial temporal arteries.

The investigations at the present time (and 4-weeks ago in brackets) were Hb: 131 (121) g/L, WCC 12.9 (9.4) x $10^9$/L; Platelets 366 (502) x $10^9$/L; CRP 19 (108) mg/L. The serum ALT and creatinine were normal. The urine was bland without protein or casts. Serum protein electrophoresis did not demonstrate a paraprotein. Ultrasonography of the superficial temporal (with 22 MHz probe) and maxillary arteries (with 8-12 MHz probe) did not demonstrate abnormalities. There was symmetrical concentric hypoechoic thickening of the intima-media complex affecting the common carotid, subclavian and axillary arteries. Both axillary arteries exhibited long stenoses between the lateral thoracic and subscapular artery (Figure 1).

The two recognised forms of large vessel vasculitis are Takayasu arteritis and giant cell arteritis (GCA). Pathologically indistinguishable, the two diseases are differentiated by age of the individual and arterial tropism. The criteria to classify individuals into these two disease groups were last published in 1990 (1, 2). This Northern European man in the 7$^{th}$ decade of his life meets the classification criteria for Takayasu arteritis but not for GCA. He has sparing of the branches of the external carotid arteries and has involvement of the aorta and its first order branches, producing a 'pulseless' phenotype. By common practice, this individual would have been easy to classify as Takayasu arteritis if he had been 20 years younger. Equally, he would have been very easy to classify as GCA if he had additional cranial artery involvement. Indeed, bilaterally arm claudicant disease has been described. (3) However, his particular phenotype of carotid, subclavian and axillary disease with pulselessness makes for an uncomfortable diagnosis that may be a result of cognitive bias. An epidemiological study of 2731 individuals with Takayasu arteritis in Korea has >25% of its participants diagnosed after the age of 60 (4). But when that same anatomical tropism is portrayed in a European country, it has been classified as being GCA (5). It is likely that are a number of individuals in Korea that could have been classified as GCA, and conversely, a number of individuals in Europe who might have met classification criteria for Takayasu arteritis.

There are many forms of cognitive bias in clinical medicine, one of them being the 'framing effect' - where the manner in which the information is presented results in different choices being made (6).

A quote attributed to Voltaire sums up the situation – "The human brain is a complex organ with the wonderful power of enabling man to find reasons for continuing to believe whatever it is that he wants to believe". Genetic, immunological, and environmental factors will be responsible for the tropism of the arterial disease. We know this from other autoimmune diseases that behave differently in different genetic groups – E.g Systemic lupus erythematosus. It is common to associate GCA as being a burden for people of Northern European ancestry. But what if being Northern European confers a genetic advantage in the form of late presentation of the disease with tropism for arteries which draw attention to its presence earlier. Alternative arguments about them being separate diseases include the difference in response to immunomodulatory treatments, acute phase response, and difference in incidence of polymyalgic symptoms. These are not arguments based upon pathological mechanisms which differentiate diseases. Just briefly if we were to accept that they might be the same disease with different phenotypes, we can apply what we have learnt from another multi-phenotype vasculitis – Granulomatosis with polyangiitis (GPA). GPA with otorhinolaryngological disease relapses more often and has lower levels of acute phase response (7, 8). If the presence of maxillary arterial involvement can cause 'jaw claudication', it is not too difficult to appreciate that the relative ischaemia of muscles around the shoulder girdle would be part of subclavian and axillary artery disease. Recent work has demonstrated that individuals with GCA have more widespread disease than was previously thought and this has been taken to mean that age should continue to assist in classifying GCA vs Takayasu arteritis. But this is not a scientifically valid principle because we have not looked at the external carotid branches in those with Takayasu arteritis to demonstrate that they are normal. We do not have data on the incidence of large vessel vasculitis in different parts of the world. The incidence of GCA is always presented in those above the age of 50, whereas that of Takayasu (when reported) is presented for the entire population. If the combined incidence of large vessel vasculitis is shown to be similar, with differences only in the phenotype, it will add gravitas to the hypothesis that these two pathologically indistinguishable diseases are not different at all. In the meantime, we present a European man with Takayasu arteritis presenting in the 7$^{th}$ decade of life with severe arterial disease affecting the aorta, common carotid, and subclavian arteries.

## Disclosure statement

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## Ethics

Informed consent has been obtained from the patient

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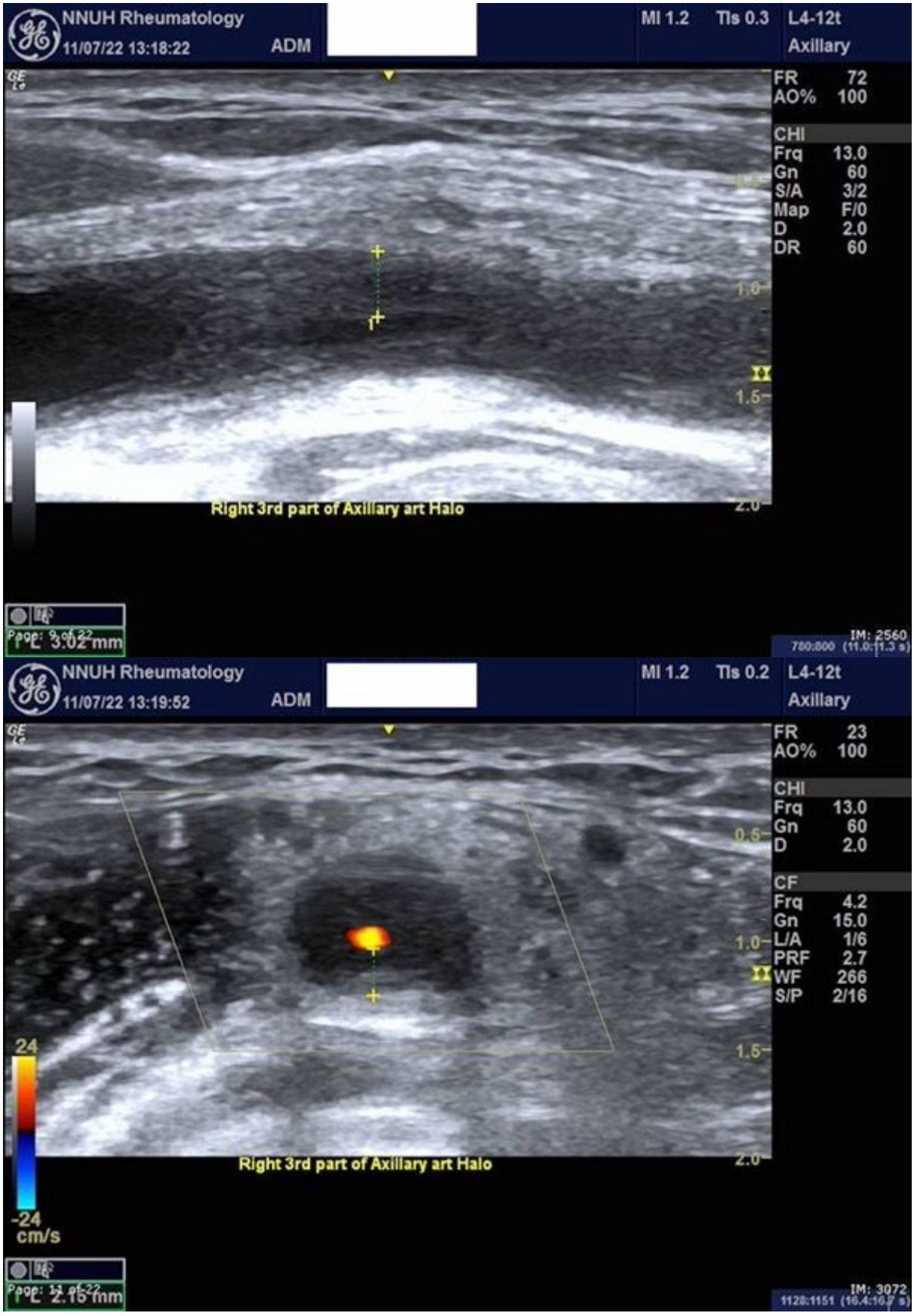


Figure 1: Ultrasonographic image of the right axillary artery acquired using a GE LOGIQ e machine with a linear 4-12 MHz probe

A) B mode longitudinal image showing thickening of the near and distant wall of the third part of the right axillary artery producing significant narrowing of the lumen; B) colour doppler transverse view of the third part of the right axillary artery showing the 'halo' sign.


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