Review Article

Carotid body disease and the physician – chronic carotid glomitis

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Summary: There are three types of histological change in the carotid bodies which appear to have physiological and clinical associations. A prominence of the dark variant of chief cells with their contents of met-enkephalin and other peptides appears to be associated with acute exposure to hypoxia. Proliferation of sustentacular cells around the clusters of chief cells appears to be related to ageing and also to systemic hypertension.

Recently we have described a new condition of chronic carotid glomitis which is characterized by follicles of lymphocytes and may have a basis in auto-immunity. In the present review we report for the first time plasma cell activity in the carotid bodies of an elderly man, especially around nerve fibrils and unmyelinated axons ensheathed in sustentacular cells. Such appearances are consistent with the view that ageing nerve fibrils may be the antigenic stimulus for the development of chronic carotid glomitis.

The normal carotid body

The carotid bodies are of great importance as chemoreceptors in acclimatization to the hypobaric hypoxia of high altitude¹ and in maintaining adjustment to this environment. The contribution of carotid chemoreceptor drive to respiration in normoxic man is uncertain but has been estimated at 15%.² However, even at sea level this level of respiratory drive induced by the carotid bodies is enhanced by the hypoxaemia resulting from heart or lung disease. There is increasing evidence to suggest that the efficiency of chemoreception may be related to visible changes in the tissue of carotid bodies.

The carotid body comprises lobules of cellular tissue separated from one another by stromal connective tissue in which ramify blood vessels and nerves.³ The blood vessels are branches of the glomic arteries which usually arise close to the carotid bifurcation. The interlobular branches are elastic in nature and resemble the carotid sinus, suggesting that they may share a baroreceptor function. They enter the lobules as muscular intralobular arterioles which appear to be capable of controlling the flow of blood to various parts of the lobule. The nerves ramifying in the stromal tissues are in part afferent branches of the glossopharyngeal, conveying chemoreceptor stimuli to the brain. The remainder are branches of the ganglio-

glomerular nerve carrying efferent branches from the superior cervical ganglion and probably involved in the control of the glomic vasculature.

The tissue within the lobules comprises a ball of ramifying thin-walled blood vessels to which are closely applied cells of two main types. Thus the lobular tissue is described as glomic. Two types of cell are found in the lobules. The first is the chief (type I) cell of which the light variant has a characteristically large round nucleus which is clear with little heterochromatin (Figure 1). Its cytoplasm is palely eosinophilic and faintly vacuolated and has an indeterminate edge. The chief cell is an amine precursor uptake and decarboxylation (APUD) cell and contains within its cytoplasm dense core-vesicles which at ultrastructural level are found to comprise a dark osmiophilic core surrounded by a clear halo.³ The core contains the peptides leu and met-enkephalins and to less extent Substance P and vasoactive intestinal polypeptide. The chief cells also contain biogenic amines including adrenaline, serotonin and especially dopamine. There are two other variants of chief cells termed dark and pyknotic cells (Figure 1). Collections of chief cells of these various types are surrounded by elongated sustentacular (type II) cells to form clusters. These sustentacular cells (Figure 2) are similar in histological and ultrastructural appearances to Schwann cells and like them they ensheath non-myelinated nerve fibrils.

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Figure 1 Section of left carotid body from a man of 31 years showing the three variants of chief cells. The light variant (arrow 1) has a large clear round nucleus with sparse heterochromatin; the cytoplasm is pale and cystic and has an indeterminate edge. The dark variant (arrow 2) has an oval nucleus in which the heterochromatin is dense; the cytoplasm is copious and shows a streamer containing small vesicles. The pyknotic variant (arrow 3) has a small compact nucleus. (H&E $\times 1500$).

Dark chief cell prominence

There are three types of histological change in the carotid bodies which appear to have physiological and clinical associations. The first is prominence of the dark chief cells with streamers of cytoplasm containing met-enkephalin which is characteristic of exposure to hypobaric hypoxia and sustained hypoxaemia and which is likely to be associated with increased hypoxic ventilatory drive (Figure 3). We have found prominent dark cells in the carotid bodies of four native highlanders from Ladakh, resident at altitudes of between 3300 m and 4200 m.⁴ They also occur in clusters of the carotid bodies of cattle taken up to abattoirs in the Andes.⁵ We have also seen dark cells in the carotid bodies of a woman of 62 years with a large ventricular septal defect and subacute reversal of the intracardiac shunt exposing the chemoreceptor to arterial oxygen unsaturation.⁶

Figure 2 Section of carotid body from a man of 61 years showing prominent sustentacular cells. They have an elongated nucleus and cytoplasm and closely resemble Schwann cells. (H&E $\times 1500$).

Sustentacular cell proliferation

Sea-level man shows pronounced hyperventilation early on exposure to the hypobaric hypoxia of high altitude.¹ The native highlander hyperventilates compared to the lowlander.¹ However, there is a progressive fall in pulmonary ventilation with age at high altitude.⁷ It is possible that this is due to hyperplasia of the sustentacular cells which press on the clusters of chief cells. We found striking proliferation of such cells in a Ladakhi highlander aged 52 years.⁴ Concentric proliferation of sustentacular cells around cell clusters of chief cells is a feature of ageing of the carotid body at sea level.⁸ Overgrowth of sustentacular cells is, however, unlikely to account for the diminished ventilatory response to hypoxia reported in all native highlanders.⁹

Sustentacular cell proliferation has an interesting association with systemic hypertension as well as with

Figure 3 Section of carotid body from a woman of 80 years with chronic obstructive lung disease associated with chronic hypoxaemia. There is focal proliferation of the dark variant of chief cells. (H&E 1500).

age. In young men with early, mild systemic hypertension, there is physiological evidence of increased sensitivity of their chemoreceptors.¹⁰ When systemic hypertension is severe and becomes established with left ventricular hypertrophy, there is a proliferation of sustentacular cells around the clusters of chief cells compressing them.¹¹ We found gross proliferation of sustentacular cells with striking compression of chief cells in a 61 year old man with coarctation of the aorta in whom there must have been severe hypertension in the upper part of the body.¹² It seems likely that progressive compression and loss of glomic cells would interfere with chemoreceptor function so that the probability is that severe systemic hypertension is likely to become associated with a falling-off of ventilatory drive. The same proliferation of sustentacular cells is seen in long standing cases of chronic obstructive lung disease.¹¹ Again in such patients ('blue bloaters') respiratory insensitivity is known to develop.¹³ All these examples suggest that proliferation of sustentacular cells, with compression of the clusters of chief cells, constitutes a second class of

tissue change in the carotid body, this time with a fall off in hypoxic ventilatory drive.

Chronic glomitis

Into this clinical setting we have recently been able to add a third type of pathology of the carotid body, in which prominent foci of lymphocytes appear in its substance.¹⁴ A sparse infiltrate of lymphocytes appears patchily or diffusely within the stroma of the glomic tissue in the majority of people over the age of 50 years and commonly this is associated with age-changes of hyperplasia of sustentacular cells and finally fibrosis and atrophy.⁸ These developments are commonly associated with progressive occlusive age-changes in the glomic arteries. In about a quarter of all subjects over the age of 50 years, the histological features are more striking for the lymphocytes form large focal aggregates up to 500 μ m in diameter. We have recently described a series of such cases and believe it constitutes a new disease which we have termed 'chronic carotid glomitis'.¹⁴ The lymphoid aggregates are round, oval or fusiform in shape and they are composed of small, round lymphocytes, transformed lymphocytes and, at the edges of the foci, a few plasma cells. Lymphoid follicle-centres were not found in our cases.

Immunological characterization of the lymphocytes reveals that diffuse infiltrates in the stroma are T-cells which also form 50 to 75% of those comprising the focal aggregates.¹⁴ It is likely that, in common with chronic inflammatory infiltrates generally, a subset ratio of 2:1 helper to suppressor cells might be anticipated.

The histological features are strikingly reminiscent of other pathological entities thought to be a manifestation of auto-immune disease. Examples are focal chronic thyroiditis,¹⁵ Hashimoto's disease, focal lymphocytic chronic sialadenitis,¹⁶ Sjögren's syndrome, auto-immune gastritis, and adrenalitis. In severe or chronic examples of auto-immune disease lymphoid follicles may form, with the full range of follicle centre cells in addition to the cell types described above. In thyroid glands affected by Hashimoto's or Graves' disease, the infiltrating population of lymphocytes between the thyroid follicles is predominantly composed of T-cells, as in chronic carotid glomitis.

In our previous report¹⁴ we speculated that, if chronic carotid glomitis is an autoimmune disease similar to focal chronic thyroiditis, one might anticipate finding examples where prominent accumulations of plasma cells were present at specific sites in the tissues. While most antibodies found in serum are produced by plasma cells in lymph nodes, spleen and bone marrow, some may be formed by plasma cells at the site of a chronic inflammatory reaction around

antigenic material. In the case of auto-immune disease the site of focal accumulations of plasma cells in a complex tissue containing several components may offer some insight into which component is degenerating and forming an antigenic stimulus.

Plasma cells in chronic glomeritis – a new observation

We have now come across such a case for the first time and it sheds an interesting insight into what may be the antigen in the carotid bodies. It occurred in a man of 81 years who died from a cardiac arrest following coronary thrombosis and a transmural infarct in the posterior wall of the left ventricle. There was intense plasma cell activity throughout the carotid bodies. Some glomic venules were surrounded by a cuffing of lymphocytes and many more by prominent collections of large, mature plasma cells (Figure 4). There were large collections of lymphocytes closely approximated to lengths of myelinated nerves coursing through the stroma of the carotid body. Small nerves, commonly

seen in transverse section, had around them an infiltrate of large, mature plasma cells (Figure 5). A severe, diffuse infiltrate of lymphocytes and plasma cells within the glomic parenchyma was situated mainly around the clusters in close proximity to the encircling sustentacular cells which ensheath the axons. The small lymphocytes and plasma cells around small glomic blood vessels and nerve fibrils proved to be, or derived from, B cells. Chronic carotid glomeritis is a disease of the elderly and aged, occurring only after the age of 50 years and affecting 29% of subjects older than 70 years. Hence it seems likely that the antigenic stimulus for the apparent auto-immune reaction is related to degenerating nerve tissue in the ageing glomus. The fibrils involved are likely to be branches of the glossopharyngeal and unmyelinated axons ensheathed by the sustentacular cells surrounding clusters of chief cells in the glomic parenchyma.¹⁷ It is likely that with involvement of the nerves in the carotid body chemoreceptor activity is compromised. To our knowledge there have been no studies of chemoreceptor function in the elderly.

Figure 4 Cuffing of plasma cells around glomic venules. (H&E $\times 600$).

Figure 5 Plasma cells congregated around nerves within the substance of the carotid body. (H&E $\times 600$).

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