Pheochromocytoma

Pheochromocytoma of the adrenal medulla and paraganglioma of the extra-adrenal sites are featured by a proliferation of chromaffin cells arranged in clustered or trabecular patterns. Pheochromocytoma secretes excessive amounts of catecholamines (adrenalin, noradrenalin and/or dopamine) to manifest 5 P's, such as pressure (hypertension), pain (headache), perspiration (sweating), palpitation and pallor. Pheochromocytoma has been known as a 10% tumor: 10% bilateral, 10% malignant, 10% extra-adrenal, 10% asymptomatic, 10% pediatric and 10% familial (inherited). The genes involved in pheochromocytoma include succinate dehydrogenase-subunit B (SDHB), von Hippel-Lindau (VHL), multiple endocrine neoplasia-2 (MEN2) and neurofibromatosis-1 (NF1). SDHB-related tumors (cluster 3) can be malignant and may secrete dopamine and noradrenalin. VHL-related tumors (cluster 1) typically produce noradrenalin, whereas MEN2 or NF1-related tumors (cluster 2) are more likely to produce adrenalin.

Ref.: Kiriakopoulos A, et al. Pheochromocytoma: a changing perspective and current concepts. Ther Adv Endocrinol Metab 2023; 14: 20420188231207544. doi: 10.1177/20420188231207544

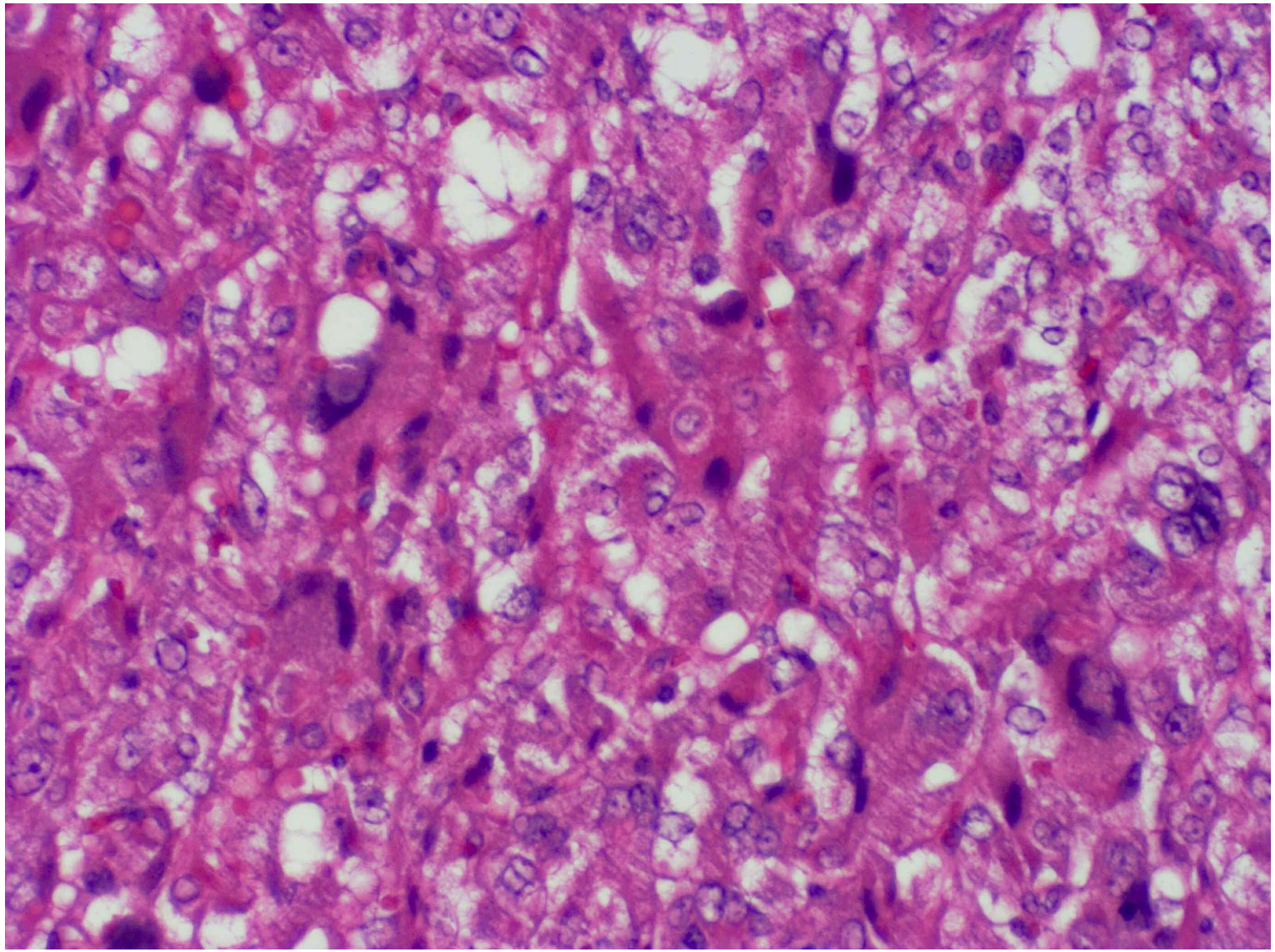
Adrenalin production in the adrenal medulla

Phenylethanolamine *N*-methyltransferase (PNMT), an enzyme converting noradrenalin (norepinephrine) to adrenalin (epinephrine), is primarily expressed in the adrenal medulla. PNMT is known to be regulated by glucocorticoids made in the adrenal cortex. The blood flow to the adrenal medulla is mainly via adrenocortical portal vein system, and, therefore, the blood circulating to the adrenal medulla contains a high concentration of corticosteroids. These are the reasons why the adrenal medulla is anatomically surrounded by the adrenal cortex and adrenalin is secreted only from the adrenal medulla. Paraganglion cells and sympathetic nerve cells lack the expression of PNMT and secrete noradrenalin alone.

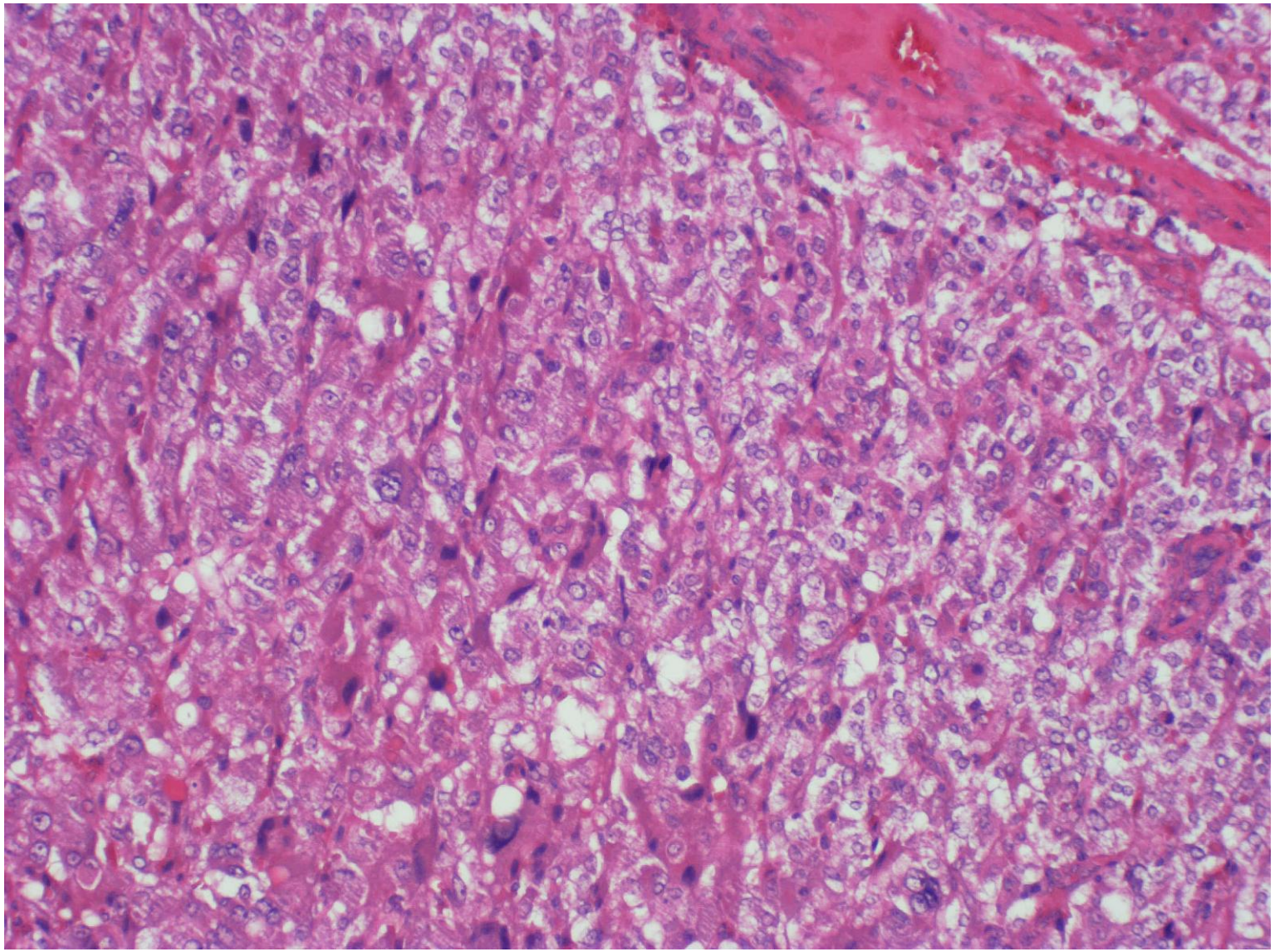
Ref.: Bauer MB, Currie KPM, Chapter 29. Adrenal medulla hormones. In: Hormonal Signaling in Biology and Medicine. Comprehensive Modern Endocrinology. 2020, pp. 635-653. doi: 10.1016/B978-0-12-813814-4.00029-8

Adrenalin or epinephrine ?

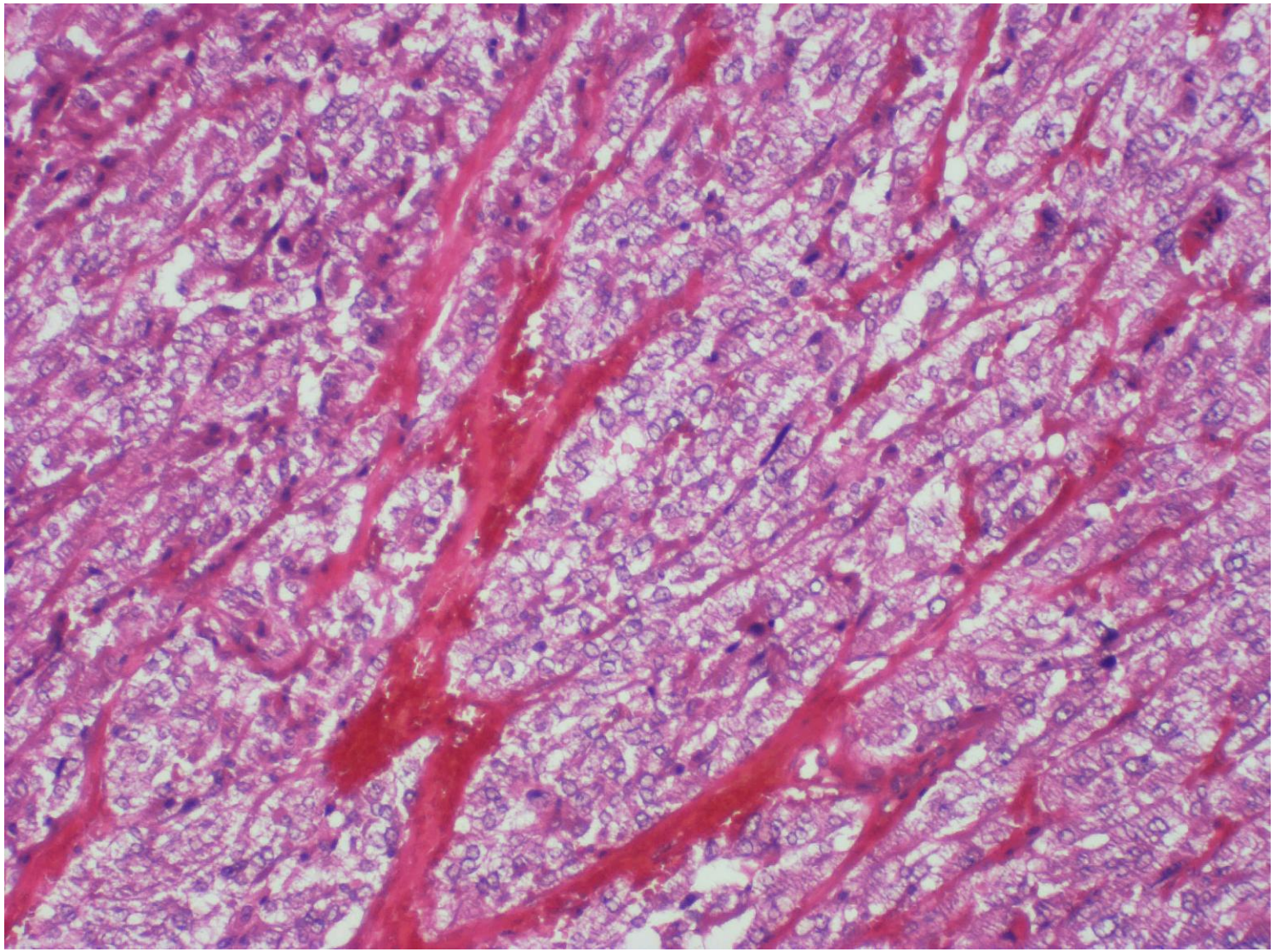
Jōkichi Takamine (1854-1922), a Japanese chemist born in Takaoka, Toyama, Japan, graduated from Tokyo Universityin 1879. In 1887, he isolated the enzyme takadiastase, an enzyme catalyzing the breakdown of starch, from Aspergillus oryzae. In 1890, he established his own research laboratory in New York City, and licensed the exclusive production rights for takadiastase to the largest US pharmaceutical company, to become a millionaire in a relatively short time. In 1901, with the aid of Mr. Toru Ichikawa, he for the first time in the world purified the glandular hormone "**adrenalin**" from the internal organs of the livestock. Adrenalin became the very first effective bronchodilator for asthma to contribute to medicine significantly. Dr. **John Jacob Abel** (1857-1938), a professor of pharmacology at Johns Hopkins University School of Medicine, had tried to isolate "**epinephrine**" from the sheep adrenal medulla, but Prof. Abel's isolate was a monobenzoyl derivative of epinephrine. While he was improving his processes on decomposing the benzoyl derivative to obtain epinephrine salts using saponification, Takamine visited Abel's lab to discuss the process of isolation. Soon, Takamine successfully isolated the neutral base of epinephrine by adding ammonium to highly concentrated extract. This visit provoking a suspicion of plagiarism actually hampered him to get Nobel Prize. In 1912, the mayor of Tokyo (Yukio Ozaki) and Jokichi Takamine, the first president of Nippon Club of New York City, gifted cherry blossom trees, to be planted in the West Potomac Park surrounding the Tidal Basin in Washington, DC. In 2006, the Ministry of Health, Labour and Welfare, Japan, decided to utilize "adrenalin" instead of "epinephrine" as an official term for this hormone in Japan, in order for regaining the Takamine's honor.



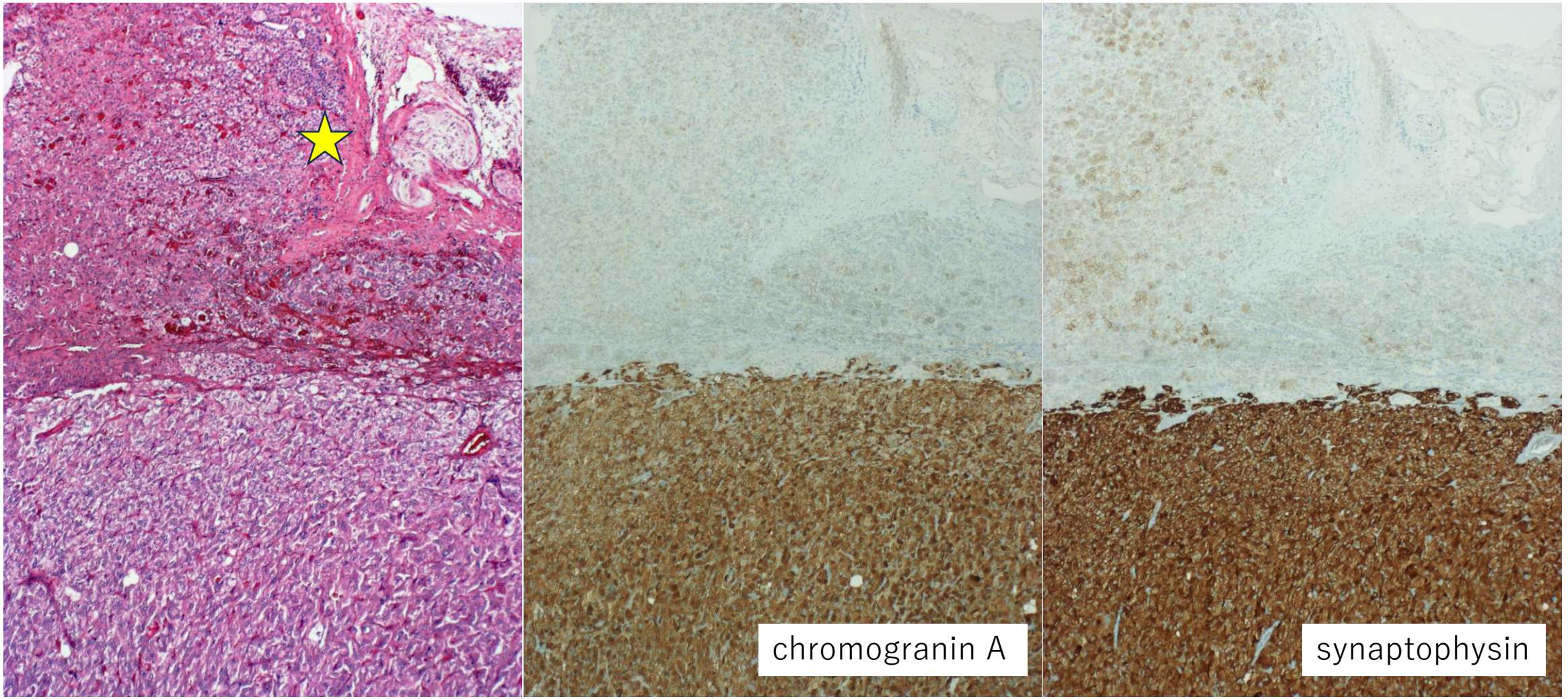
Pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient. The tumor cells possess eosinophilic granular cytoplasm. The nuclei show mild size variations (H&E-1).



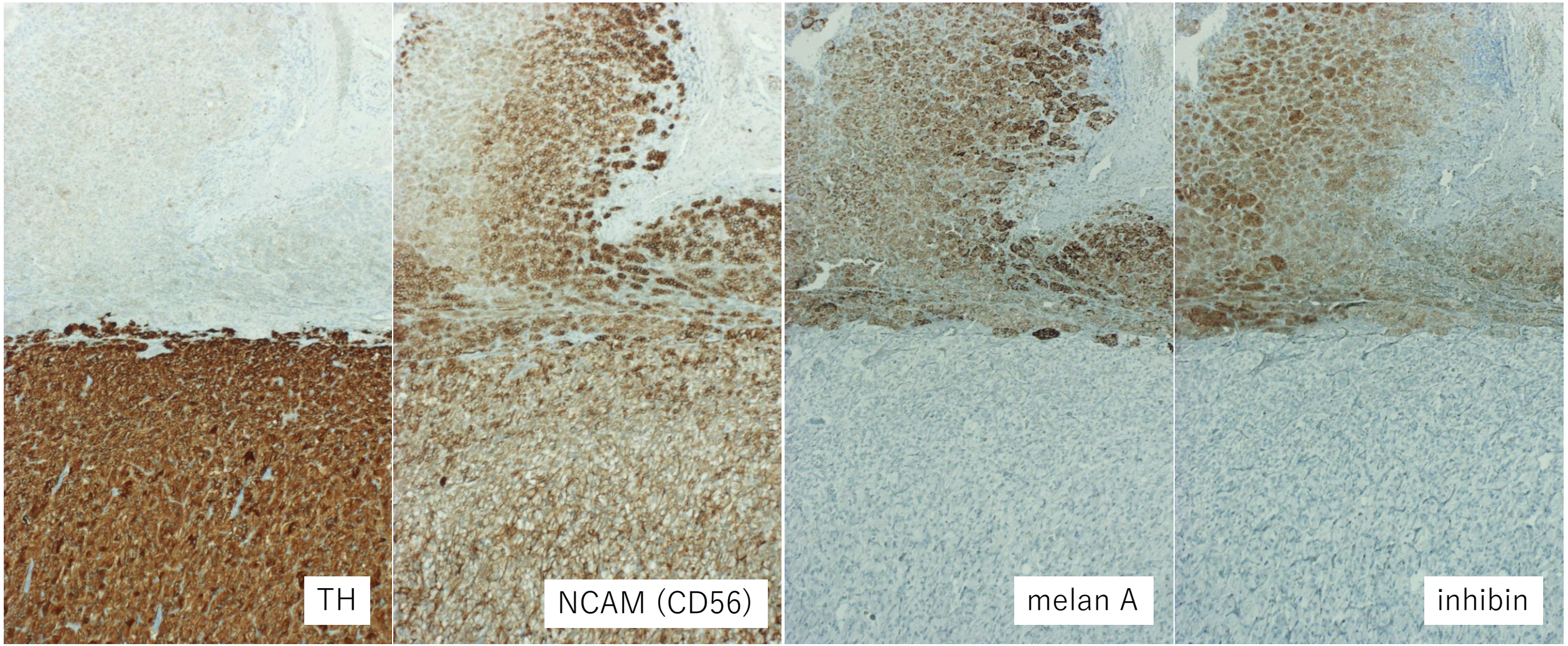
Pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient. The tumor cells possess eosinophilic granular cytoplasm. The nuclei show mild size variations (H&E-2).



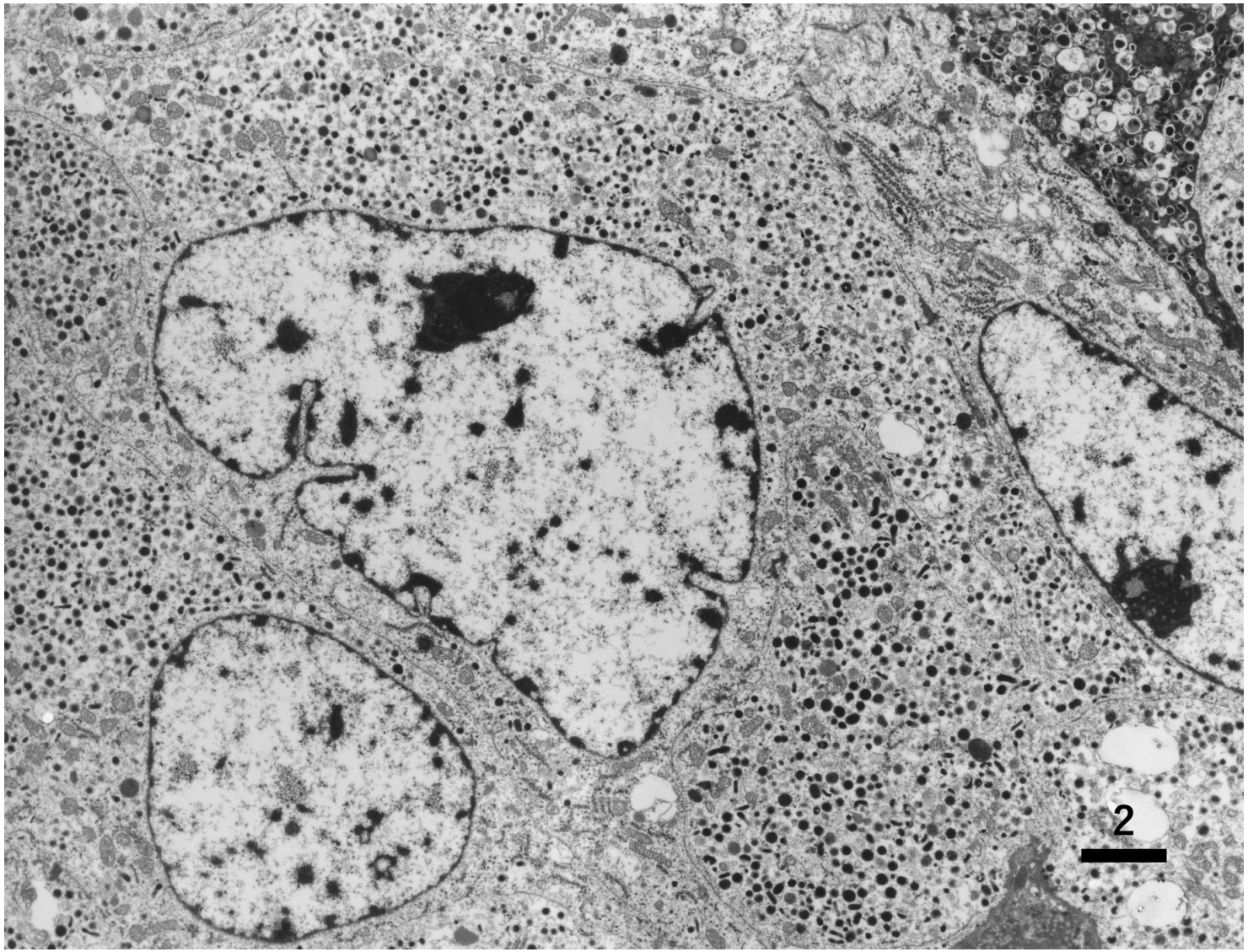
Pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient. The tumor cells possess eosinophilic granular cytoplasm. The nuclei show mild size variations. Vascularity is rich (H&E-3).



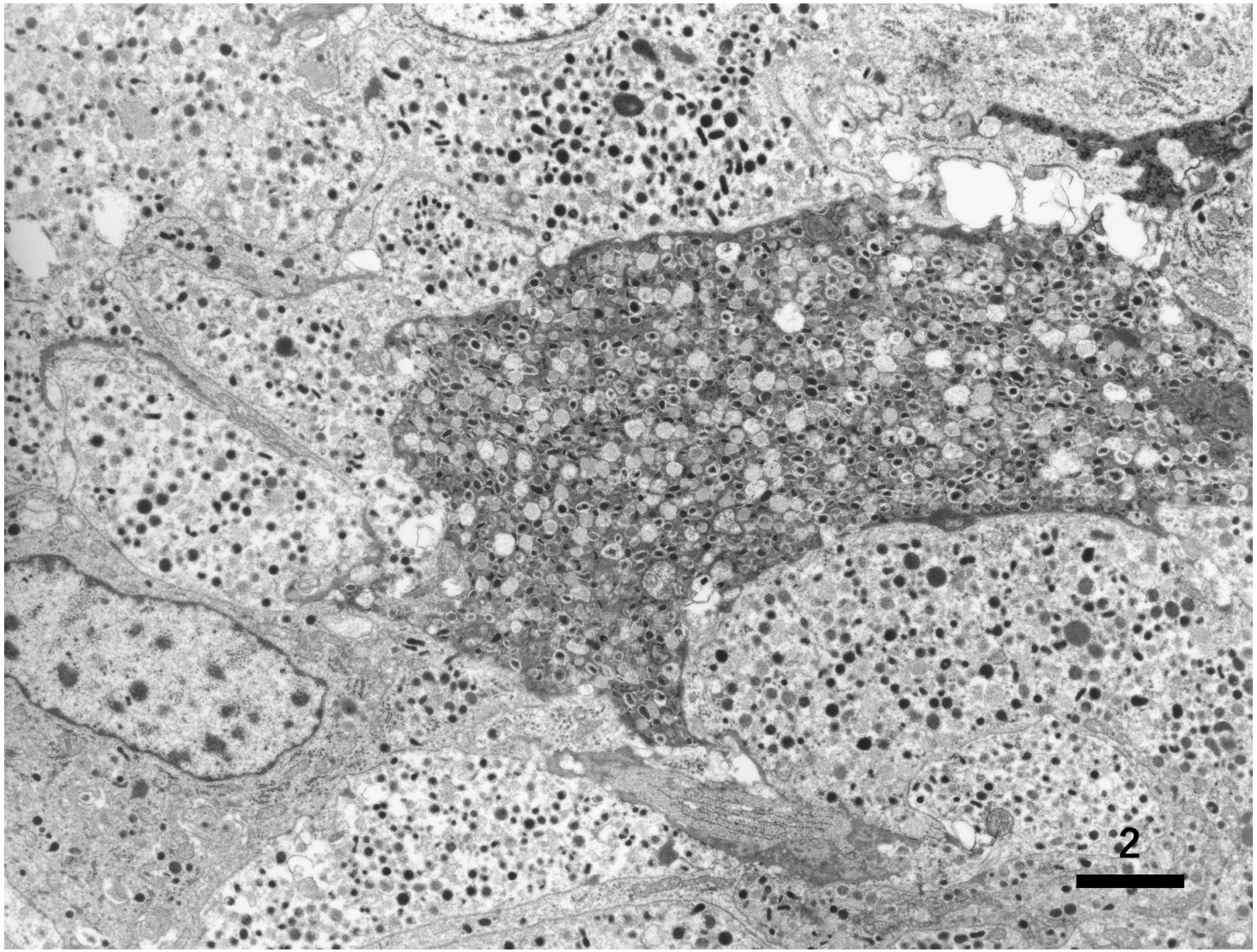
Pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient (left: H&E). The tumor cells in the lower part of the figures diffusely express chromogranin A (center) and synaptophysin (right) (immunostaining). Asterisk (the upper part of the figures) indicates the adrenal cortex.



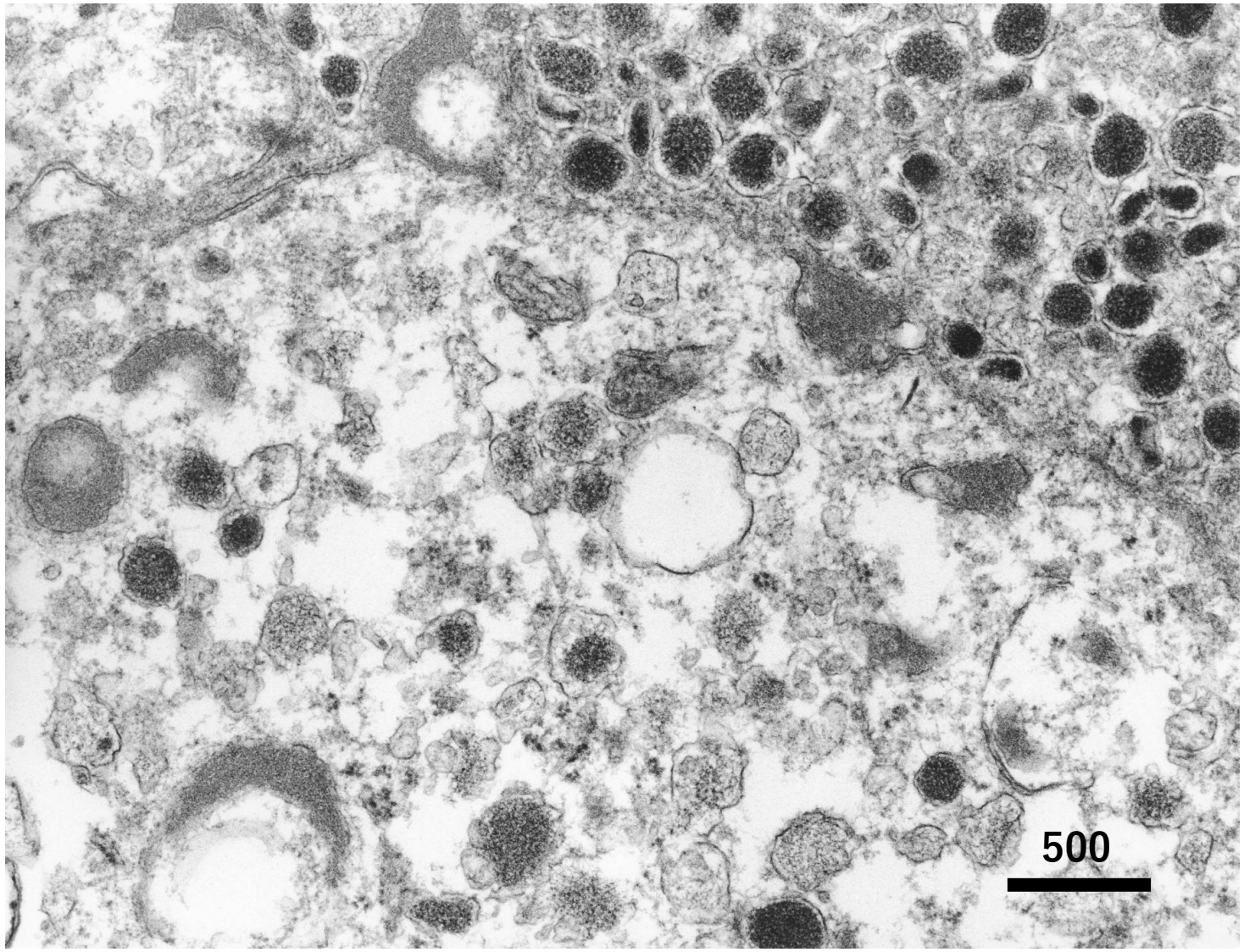
Pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient (left: H&E). The tumor cells in the lower part of the figures diffusely express tyrosine hydroxylase (TH) (left). NCAM (CD56) is expressed both in the pheochromocytoma and adrenal cortex (the upper part of the figures). Melan A and inhibin are positive in the adrenal cortex, while pheochromocytoma is negative (right two) (immunostaining).



Ultrastructure of pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient. The tumor cells possess numerous neuroendocrine granules in the plump cytoplasm (TEM-1).

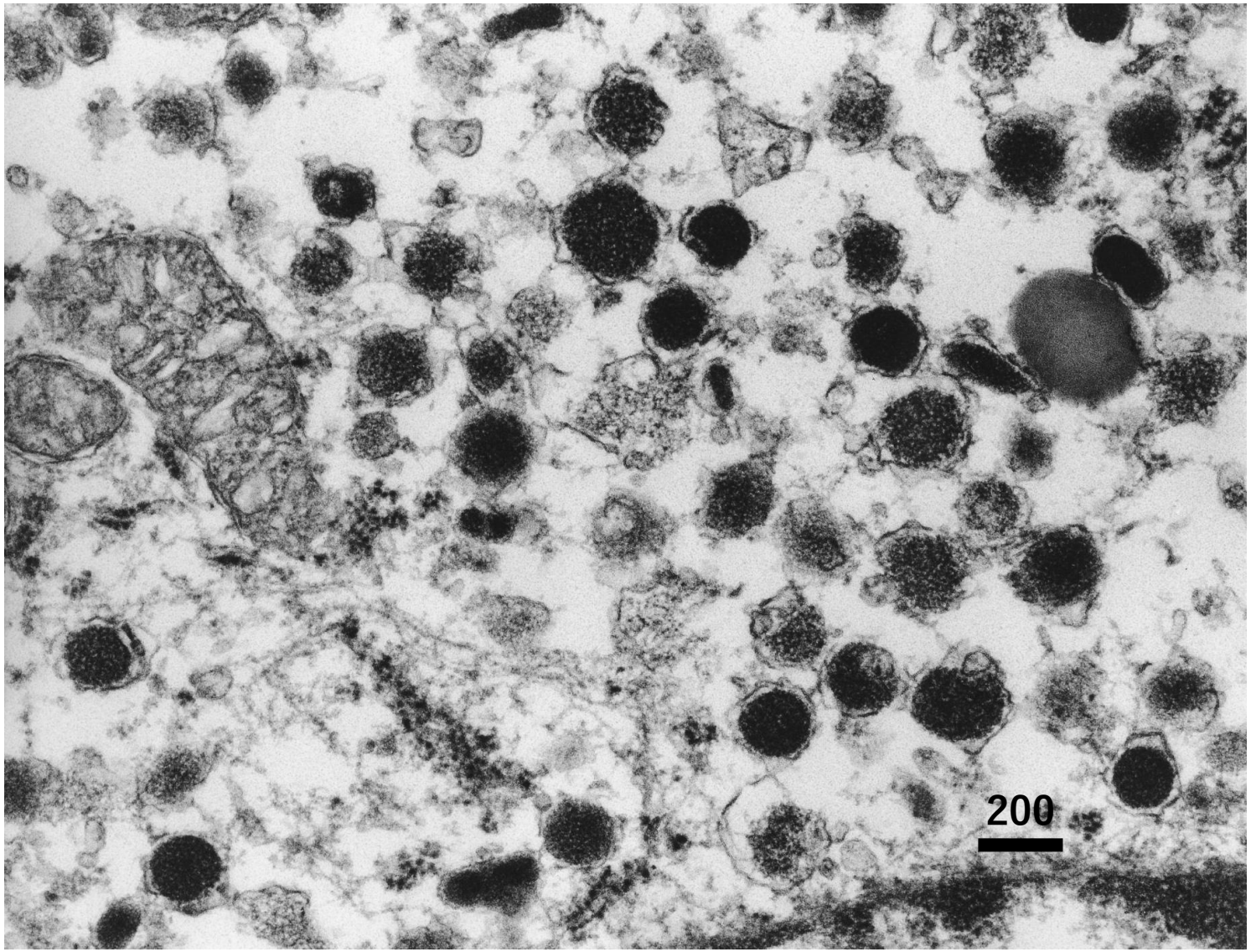


Ultrastructure of pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient. Two types of tumor cells can be recognized: one (NA type) has electron-dense granules, while another (A type) possess electron-lucent granules with denser cytoplasmic background (TEM-2).



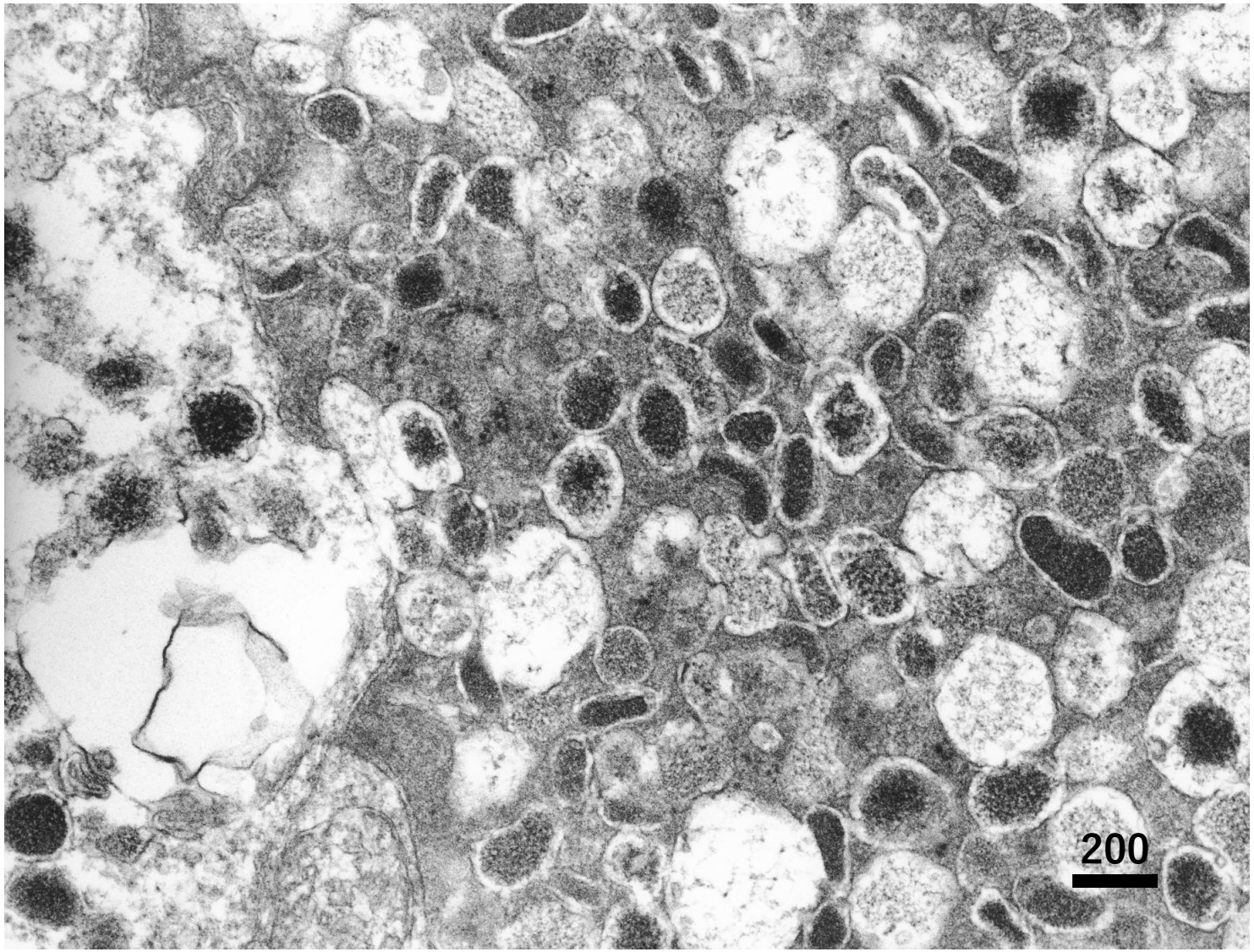
Ultrastructure of pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient. Two types of tumor cells can be recognized: one (NA type, containing noradrenalin) has electron-dense granules, while another (A type, containing adrenalin) possess electron-lucent or less electron-dense granules. The granules measure 140-360 nm with the mean of 210 nm (TEM-3).

NA type cell



Ultrastructure of pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient. The NA (noradrenalin) type cell has electron-dense granules, measuring 140-360 nm with the mean of 210 nm (TEM-4).

A type cell



Ultrastructure of pheochromocytoma of the adrenal medulla seen in a 78 y-o female patient. The A (adrenalin) type cell has less electron-dense or electron-lucent granules, measuring 140-360 nm with the mean of 210 nm. Some granules are elongated (TEM-5).