PATHOLOGICA 2025;117:173-177**;**
DOI: 10.32074/1591-951X-1054ER

ERRATA CORRIGE

This is the correct version of the article:
Campora M, Negri G, Longari V, et al. Cholesterol granuloma. Pathologica 2025;117:55-59. https://doi.org/10.32074/1591-951X-1054

Letter to the Editor

Cholesterol granuloma. Another brick in the wall of mediastinal lesions

Michela Campora[1], Giampiero Negri[2,3], Virgilio Longari[4], Maurilio Ponzoni[1,3]

[1] Pathology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [2] Department of Thoracic Surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy; [3] Vita-Salute San Raffaele University, Milan, Italy; [4] Nuclear Medicine Unit, IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy

Dear Editor-in-Chief,

A 57-year-old man underwent about two years ago a coronary arterial bypass and a total thyroidectomy for ischemic heart disease and diffuse multinodular goitre, respectively. A routine follow-up cardiac magnetic resonance imaging (MRI) revealed the presence of a newly developed, expansive lesion in the anterior mediastinum. This lesion was further investigated by total body computed tomography (CT) scan, which showed a 22x20 mm mediastinal lesion, with a lymph node measuring 8 mm in maximum diameter within the adjacent fat tissue. A further MRI confirmed the presence of both mediastinal and lymph node findings, rais-

Received: July 17, 2024
Accepted: October 23, 2024

Correspondence
Michela Campora
E-mail: mikycampora@yahoo.it

How to cite this article: Campora M, Negri G, Longari V, et al. Cholesterol granuloma. Pathologica 2025;117:173-177. https://doi.org/10.32074/1591-951X-1054ER

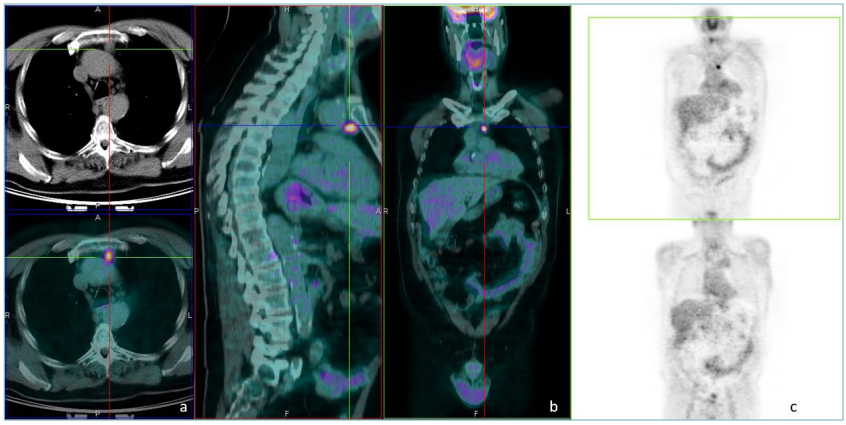

Figure 1. 18F-FDG PET/CT examination was performed with 3D (emissive) technique, fasting and 60 minutes from the injection of FDG, examined with transaxial, sagittal and coronal reconstructions 5 mm thick (a,b), with and without body attenuation correction, and documented with coronal slices of 10 mm contiguous, corrected for attenuation (c).18F-FDG PET/CT highlighted an increase tracer uptake in the mediastinum, in correspondence with the nodule detectable on CT images anterior to the ascending tract of the aortic arch.

ing the strong suspicion of heteroplastic lesion. One month later, a whole-body positron emission tomography (PET) scan using 18F-fluorodeoxyglucose (FDG), showed a 7.8 maximum SUV uptake in the anterior mediastinum, corroborating the above-reported findings (Fig. 1). Additional physical signs or symptoms, or laboratory alterations were absent.

On these grounds, the patient underwent thoracic surgery. A 12 mm thoracoscopic access, performed at the 8th intercostal space along anterior axillary line, revealed abundant mediastinal fat tissue. Above the aortic arch, a polylobate, reddish, non-capsulated lesion was identified and biopsied for intraoperative histopathological examination; frozen intraoperative sections revealed cholesterol cleft and a foreign body reaction including macrophages and multinucleated giant cells. The lesion was entirely excised along with adjacent fat tissue and sent for final, post-surgical classical histopathological evaluation. Our Pathology Lab received a mass measuring 3,5x2.5x1 cm, well-circumscribed and red-to-brownish on cut surface. An accomplishing portion of adipose tissue measuring 2.3 cm was present. The entire specimens were embedded and examined.

Histopathological examination revealed a lesion invariably composed of cholesterol clefts, foreign body-type giant cells and minimal inflammatory reaction, at variance with usual significant degree of chronic inflammation usually accomplishing granulomas. In detail, low power magnification highlighted a geometric architecture composed of small nests of cholesterol clefts surrounded by ill-defined fibrous bands containing a foreign body reaction; at higher magnification, the intervening fibrous stroma contained multinucleated giant cells in varying proportions, which were admixed with a minimal, whenever present, amount of inflammatory infiltrate, mainly composed of small lymphocytes and plasma cells. In some areas, cholesterol clefts were closely proximal to or admixed with remnants of thymic tissue (Fig. 2). Cytologic atypia, mitotic activity, necrosis, or haemorrhagic foci were absent. The diagnosis of cholesterol granuloma (CG)

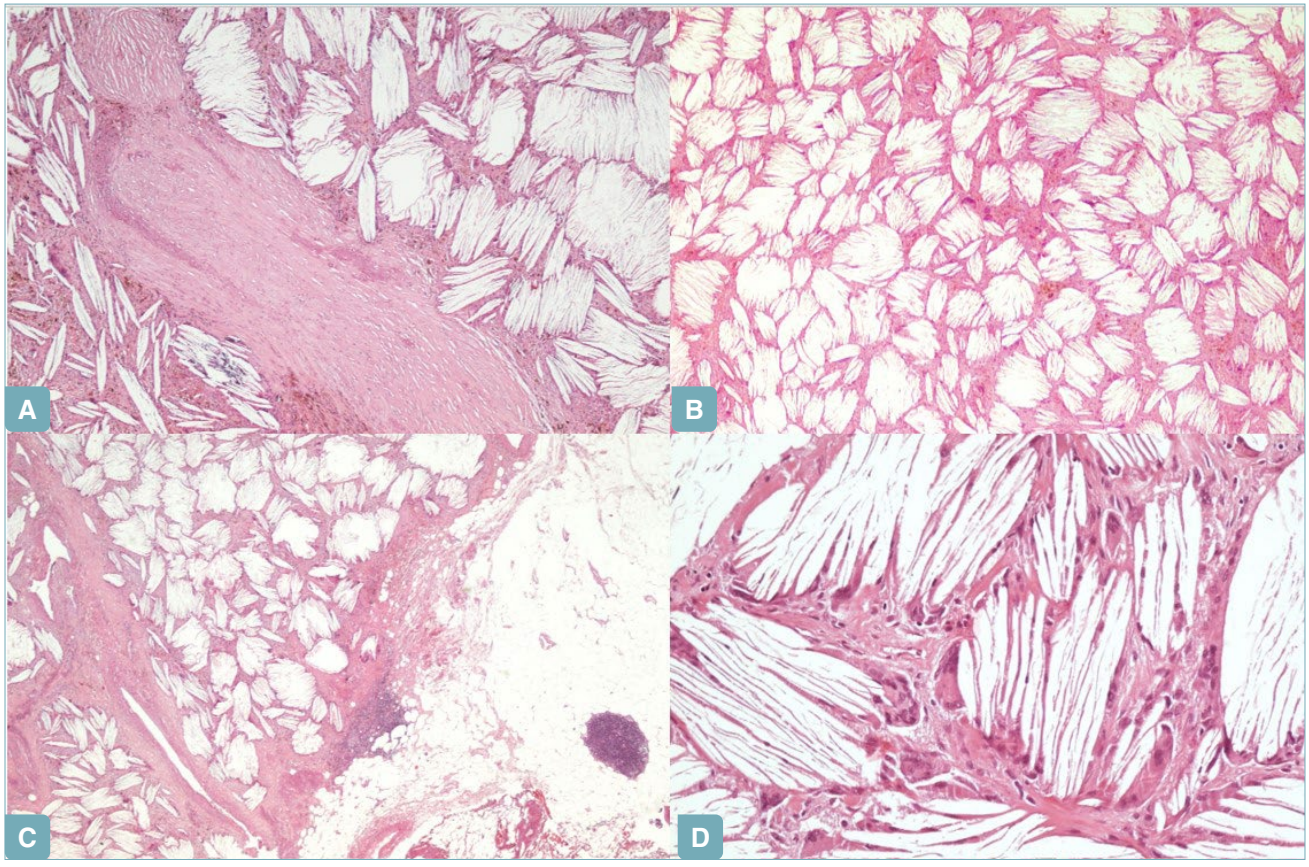

Figure 2. Cholesterol granuloma on hematoxylin and eosin: clusters of lipid crystals surrounded by foreign body reaction and hemosiderophages interspersed in dense connective tissue or fibrosis (A,B); cholesterol clefts proximal to thymic tissue remnants (C); multinucleated giant cells and histiocytes surrounding cholesterol clefts (D).

Table I. Review of the literature of mediastinal cholesterol granulomas.

Author	Y/sex	cm	Mediastinum	Gross appearance	Previous surgery/ trauma	Comorbidities / symptoms	Imaging
Manabe [6]	71 F	4.2, 3.2, 2.6 2.3 Multiple lesions	Anterior	Four lesions in the thymus with elastic hardness and yellowish-brown discoloration	Surgical procedure for an aneurysm of the aortic arch	Dyslipidemia, hypertension, aortic aneurysm, coronary artery stenosis, old cerebrovascular infarction	CT: slight contrast enhancement tumor with spotty calcification
Nagata [7]	56 F	2.0, 1.3 two lesions	Anterior	A cystic lesion containing yellowish-brown jellied effusion and a light-brown, solid nodule were observed separately in the thymus.	No history of trauma/ surgery	Dyslipidemia	CT: non-contrast enhancement lesion PET: increased uptake
Drury [8]	74 M	3.2	Anterior	Consistent with thimyc tumour	No	Paroxysmal atrial fibrillation, COPD	PET: lesion with maximum uptake 13.7, with a central area of inactivity
Ghigna 1 [9]	53 M	5	Anterior		*	*	*
Ghigna 2 [9]	25 M	4	Anterior		*	*	*
Weissferdt 1 [10]	58-71	range 2-6	Anterior	The main masses were surrounded by yellowish adipose tissue in all cases.	*	Cardiac problems	*
Weissferdt 2 [10]	58-71		Anterior	Necrosis and hemorrhage were not described in any of the lesions.	*	Barrett's esophagus	*
Weissferdt 3 [10]	58-71		Anterior	*	*	Cough and dyspnea	*
Weissferdt 4 [10]	58-71		Anterior	*	*	Completely asymptomatic mass discovered during routine chest imaging	*
Krishnan [11]	65 M	2×1.9×1	Anterior	Firm, circumscribed	Incidental finding of an anterior mediastinal mass overlying the innominate vein, noted following median sternotomy during elective coronary artery bypass graft surgery.	Symptoms suggestive of exertional angina.	Coronary angiography showed an isolated 75% stenosis of the left coronary ostium.

Ezzat [12]	75 M	3x3x2	Anterior	A pair of firm, well circumscribed masses in the anterior mediastinum and thymic remnants, with granular cut surfaces. One of the nodules was diffusely hemorrhagic and focally calcified, while the other was yellow and fatty.	Incidentally during urgent coronary artery bypass graft surgery.	History of angina, hypertension, peripheral vascular disease, smoking addiction, chronic obstructive pulmonary disease, dyslipidemia, and a remote motor vehicle collision had undergone urgent coronary artery bypass graft for acute non-ST elevation myocardial infarction.	Pre-operative chest radiography showed a questionable density in the anterior mediastinum that was attributed to a shadowing effect of the first rib
Fujimoto [13]	62 M	2.0x1.8	Anterior	A nodule not associated with the thymus. A whitish-yellow or brown at cut surface with multiple calcified areas		Asymptomatic - incidentally discovered during a complete health examination	Abnormal FDG uptake: maximum of 3.3, mean of 1.9. T1-T2-weighted MRI: markedly hypo-intense lesion with irregular margin and not encapsulated. Contrast-enhanced dynamic MRI: gradually upward and weak enhancement pattern.
Luckraz [14]	74 M	2.7x2x0.7	Superior edge of the right half of the split manubrium	Brown and yellow discoloration	Elective aortic valve replacement.	Aortic stenosis and bilateral testicular lumps	Abdomen TC unremarkable
Campora	57 M	3.5x2.5x1	Anterior mediastinum	Well-circumscribed nodule, red-to-brownish on cut surface	Coronary arterial bypass and total thyroidectomy	Ischemic heart disease and diffuse multinodular goitre	CT: 22x20 mm mediastinal lesion, with an 8 mm adjacent lymphnode. MRI: confirmed the presence of both. PET: 7.8 maximum SUV uptake in the anterior mediastinum

* missing information.

was made.

CG is a well-characterized entity composed of a foreign-body giant cell-reaction developing in response to the formation of cholesterol crystals. This disease is usually diagnosed in the petrous apex of mastoid bone [1] and more rarely in the middle ear [2], where it is associated with chronic inflammation conditions like cholesteatoma and otitis media. Mediastinum is

very rarely involved by CG; the first case described by Luckraz in 2006 [3] has been followed by 8 additional reports in the English literature (Tab. I). To the best of our knowledge, the present case adds hitherto unreported details about intraoperative features and data of imaging studies.

The spectrum of differential diagnoses of anterior mediastinal masses is usually related to patient's age. Accordingly, lymphoma (either Hodgkin or non-Hodgkin) or a germ cell tumor will be the main diagnostic hypotheses in younger patients, whereas thymoma or thymic carcinoma are more likely in older patients. Thymomas with broad necrotic areas and/or cystic component may exhibit substantial tumor regression, showing cholesterol clefts and hematoidin deposits due to inflammation and absorption processes.

The actual etiology of CG is presently unknown. Many Authors [4-5] speculate about a post-traumatic or -inflammatory origin, following haemorrhage and leakage of cholesterol from damaged cell membranes and leading to an immune response with multinucleated giant cells. Along with this hypothesis, the case herein reported shows an history of previous surgery in this anatomical site. The prominent foreign body giant cell reaction in CG is not usually accomplished by a consensual abundant chronic inflammatory infiltrate; further studies are needed in order to assess whether this peculiar property could be used as a discriminatory criterion in the differential diagnosis with chronic mediastinitis, because the clinical and therapeutic implications of the latter deserve a correct diagnosis. Equally important, the awareness of this lesion during intraoperative sessions may avoid the misdiagnosis with thymic lesions. The same problem may also arise, given the presence of thymic remnants in the surrounding tissue, also during the interpretation of small biopsies obtained by mediastinoscopy and underlines the importance of correlating a complete patient's history with microscopic observations, to improve routine diagnostic practice skills. It should be emphasized that, presently, the final diagnosis of CG must rely on complete surgical resection and detailed post-surgical histological evaluation. The awareness of the occurrence of cholesterol granuloma among mediastinal lesions, albeit uncommon, avoids the misdiagnosis of chronic mediastinitis.

Acknowledgements

We wish to acknowledge the patient himself for his pugnacious spirit and his contribution in collecting the complete history, images and data.

Conflicts of interest statement

Authors have no conflict of interest to declare.

Funding

Authors have no funding to declare.

Authors' contributions

M.C. and M.P. analysed the specimen in all the diagnostic phases, conceived, designed and wrote the article. G.N. performed the surgery and contributed to the interpretation of the clinical results. V.L. carried out the imaging.

All authors provided critical feedback on the manuscript.

Ethical consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from the patient for study participation and data publication.

References

1 Hoa M, House JW, Linthicum FH, et al. Petrous apex cholesterol granuloma: pictorial review of radiological considerations in diagnosis and surgical histopathology. J Laryngol Otol. 2013;127(4):339-348. https://doi.org/10.1017/S0022215113000091.

2 Kuruma T, Tanigawa T, Uchida Y, et al. Large Cholesterol Granuloma of the Middle Ear Eroding into the Middle Cranial Fossa. Case Rep Otolaryngol. 2017;2017:4793786. https://doi.org/10.1155/2017/4793786.

3 Luckraz H, Coulston J, Azzu A. Cholesterol granuloma of the superior mediastinum. Ann Thorac Surg. 2006;81:1509–1510. https://doi.org/10.1016/j.athoracsur.2005.03.019.

4 Juanpere S, Cañete N, Ortuño P, et al. A diagnostic approach to the mediastinal masses. Insights Imaging. 2013;4(1):29-52. https://doi.org/10.1007/s13244-012-0201-0.

5 Marino M, Ascani S. An overview on the differential diagnostics of tumors of the anterior-superior mediastinum: the pathologist's perspective. Mediastinum. 2019;3(0).

6 https://doi.org/10.21037/med.2018.12.01.