Editorial

Lipofibroadenoma and other rare thymic tumors: a call for misfits

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Comment on: den Bakker MA, Vermeulen MA, van de Ven CP, *et al*. Asymptomatic lipofibroadenoma in a 17-year-old male: a case report and literature review of a rare entity. Mediastinum 2022. doi: 10.21037/med-22-32.

Keywords: Lipofibroadenoma; thymic tumor; thymectomy

Received: 22 January 2023; Accepted: 21 March 2023; Published online: 30 March 2023.
doi: 10.21037/med-23-4
View this article at: https://dx.doi.org/10.21037/med-23-4

In this article, den Bakker *et al*. showed a case of lipofibroadenoma of the thymic gland, an extremely rare primary thymic tumor with only thirteen cases reported in the literature (1). This tumor is commonly described as a thymic tumor strongly resembling breast lipofibroadenoma (2). The 2021 World Health Organization (WHO) classification of thymic tumors includes this entity into the group of thymic epithelial tumors (TET), being the only one defined as benign (keep in mind that after the 2015 WHO classification, all thymomas have to be considered as epithelial malignant tumors) (3).

In the reported cases, this tumor is described as a large intrathoracic fatty mass in young patients. This is one of the differences with thymomas, whose peak of incidence is between 50 and 60 years of age (4).

Its origin is uncertain, sometimes being considered as a hamartomatous process and in others being part of a spectrum of thymic adipose tumors such as thymolipoma. The reason for considering lipofibroadenoma as a benign tumor relies on pathologic characteristics, such as absence of atypia, conspicuous proliferative activity, and necrosis (1). Only Aydin *et al*. described signs of invasion of the mediastinal fat (5).

There are no differences in computed tomography (CT) scan or positron emission tomography computed tomography (PET-CT) scan to clearly discriminate this tumor from other thymic tumors (6). This scenario suggests that total thymectomy would be the recommended surgical resection for definitive diagnosis and treatment in these cases, as it is in thymomas (7).

The relationship between thymic lipofibroadenoma, B1 thymoma and autoimmune diseases is noteworthy. Four cases were associated with B1 thymoma and two patients presented with concurrent autoimmune disease, one anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis and the other with pure red cell aplasia and B1 thymoma (1). Whether this relationship is significant or not has a simple answer: we do not have enough information. What we know is that the indicated type of resection in B1 thymoma is total thymectomy, which is another argument to perform this technique instead of thymomectomy in lipofibroadenoma.

During the follow-up time of all the published cases (maximum 4 years) no recurrence of the disease or mortality was detected (1). Recurrence and survival are often extrapolated from retrospective studies about the oncologic behaviour of thymoma (5,8,9). Taking into account the peculiar behavior of thymoma, especially concerning its pattern of recurrence, a longer follow-up could be recommended to ensure that thymic lipofibroadenoma is a benign tumor.

A light in the dark has been kindly offered by den Bakker *et al*. with their molecular analysis, hoping to contribute to the integrated genomic landscape of TET, pioneered by Radovich *et al*. (10). No relevant somatic mutations or genetic rearrangements were identified. This is important because we know that the HMGA-2 mutation described in thymolipoma and GTF2I mutation linked to thymomas A and AB are not present in lipofibroadenoma (1,10). However, we need more information to confirm this

genomic pattern.

The constitution of the International Thymic Malignancy Interest Group (ITMIG) in 2010, led by Frank Detterbeck, was a fundamental initiative to build a worldwide multidisciplinary community willing to participate in a global database that has been crucial for obtaining evidence-based information about thymic malignancies, even refining WHO histological classification (11,12).

The ITMIG study published in 2014 by Huang *et al.* relied on a large international database filled with retrospective data of 47 institutions spanning 15 countries, with a total of 6,097 cases recorded over a 6-month period. In this case, only patients with thymoma, thymic carcinoma, or thymic carcinoid were included (13). Another surprising publication was the Réseau tumeurs THYMIques et Cancer (RYTHMIC) prospective cohort. Beyond its objectives and results, the fact is that the national network of thymic epithelial malignancies in France was able to register a total of 2,600 patients with TET in a period of 6 years (14). Any of these studies included rare thymic tumors such as lipofibroadenoma.

These initiatives suggest that thymic tumors are a rare disease, and some histologic types are commonly underreported. Additionally, these entities are often excluded from studies in order to obtain more consistent results. More information is needed in order to better determine the epidemiology, clinic, treatment and prognosis. The little evidence we have on lipofibroadenoma and other rare thymic tumors suggest that the entire scientific community has to make an effort to report these cases to improve our knowledge about them, because it seems that these "misfits" have something to say.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Mediastinum*. The article did not undergo external peer review.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-4/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/med-23-4
Cite this article as: Planas G, Trujillo-Reyes JC, Martínez-Téllez E, Libreros A, Belda J. Lipofibroadenoma and other rare thymic tumors: a call for misfits. Mediastinum 2023;7:11.