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Case report

Concurrent presence of primary hemangioma and breast cancer metastasis within a lymph node: a case report inspired by the legacy of Professor Juan Rosai

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Summary

Secondary neoplastic lesions in lymph nodes are predominantly metastases from solid tumors, whereas primary lymph node hemangiomas are exceptionally uncommon, with only 24 well-documented cases in the literature. Histologically, they are characterized by endothelial cells that may appear flattened or enlarged, with variable vascular density, and the presence of stromal elements. Notably, the concurrent presence of a primary hemangioma and a metastasis from breast cancer – the latter being the most prevalent secondary lesion in axillary lymph nodes – represents an unprecedented observation. The unique case presented herein underscores the exceptional rarity of primary lymph node hemangiomas and demonstrates for the first time their possible coexistence with breast cancer metastasis within the same axillary lymph node. In sharing and discussing this case study, we pay homage to Professor Juan Rosai, whose work in redefining rare and complex diagnoses continues to enlighten our understanding of lymph node vascular lesions.

Key words: hemangioma, axillary lymph node, breast cancer, metastasis

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Introduction

Hemangioma of the lymph node is an uncommon vascular tumor mostly observed as secondary lesions, arising from contiguous infiltration of an extranodal hemangioma [1, 2]. In comparison to their secondary counterparts, primary lymph node hemangiomas are even more exceptional occurrences, with only 24 cases documented in the literature since the first description by Gupta in 1964, as shown in Table I [3,4-16]. Their rarity bestows upon the diagnosis a remarkable complexity, underscored by the illustrative case presented by Goldstein and Bartal in 1985 [16]. Initially designated as an intranodal hemangioendothelioma, this case underwent reclassification by Professor Juan Rosai and colleagues in 1994 [2]. This reevaluation followed their 1992 case series, which still stands as the only existing collection of lymph node hemangioma cases in the literature to date [13]. Within this work, the authors also undertook the reclassification of a lymph node exhibiting "hypervascularity", a finding initially reported by Lott and Davies in 1983 [17]. This reclassified case marked a significant milestone, as it represents the first instance of a solitary lymph node hemangioma supported by sufficiently high-quality images. Hemangiomas found within lymph nodes typically show well-defined bor-

ders and are concentrated around the hilum or medulla of the lymph node. The unaffected parenchyma of the lymph node remains intact and might display slight follicular hyperplasia. This type of lesion is composed of benign single-layered and flat endothelial cells, except in the case of epithelioid hemangiomas where the endothelial cells tend to be plump. The vascular channels within hemangiomas can either be empty or filled with blood, while their stroma might range from edematous to fibrotic. These tumors can be categorized as capillary, cavernous, or mixed [1]. Capillary-type neoplasms manifest as a cluster of small blood vessels, resembling a pyogenic granuloma or canonical granulation tissue. On the other hand, cavernous hemangiomas consist of larger, irregular spaces filled with erythrocytes and occasional partially organized thrombi. Endothelial cells of hemangiomas exhibit immunoreactivity for vascular markers like CD31, CD34, Wilms tumor 1 (WT1), ETS-related gene (ERG), Friend leukemia integration 1 (FLI1), and factor VIII-related antigen (aka von Willebrand Factor).

Previous observations of carcinoma coexisting within extranodal hemangiomas have been reported [18]. However, a critical void in our current understanding revolves around the possible coexistence of hemangiomas and synchronous metastases from solid tumors within a single lymph node. This gap signifies an absence of comprehensive insights into the mechanisms, underlying factors, and potential interactions that underpin the concurrent presence of these two distinct entities within the same anatomical site. Here, we present a unique case of primary lymph node hemangioma identified in an axillary lymph node alongside synchronous metastasis from breast cancer.

Case report

A 47-year-old woman was diagnosed with moderately differentiated invasive breast cancer of non-special type (ductal) with clinically positive ipsilateral axillary lymph nodes. No neoadjuvant chemo/radiotherapy interventions were undertaken, and the patient underwent total mastectomy with lymphadenectomy. The tumor was situated in the superior-exterior quadrant of the left breast, measuring 9.5 cm in its largest dimension, and exhibited a hormone receptor (HR)+/HER2-negative phenotype.

Histopathological analysis of the axillary lymph nodes confirmed carcinoma metastasis in four level I lymph nodes and one level II lymph node. Interestingly, within the metastatic level II lymph node, a distinct, well-de-

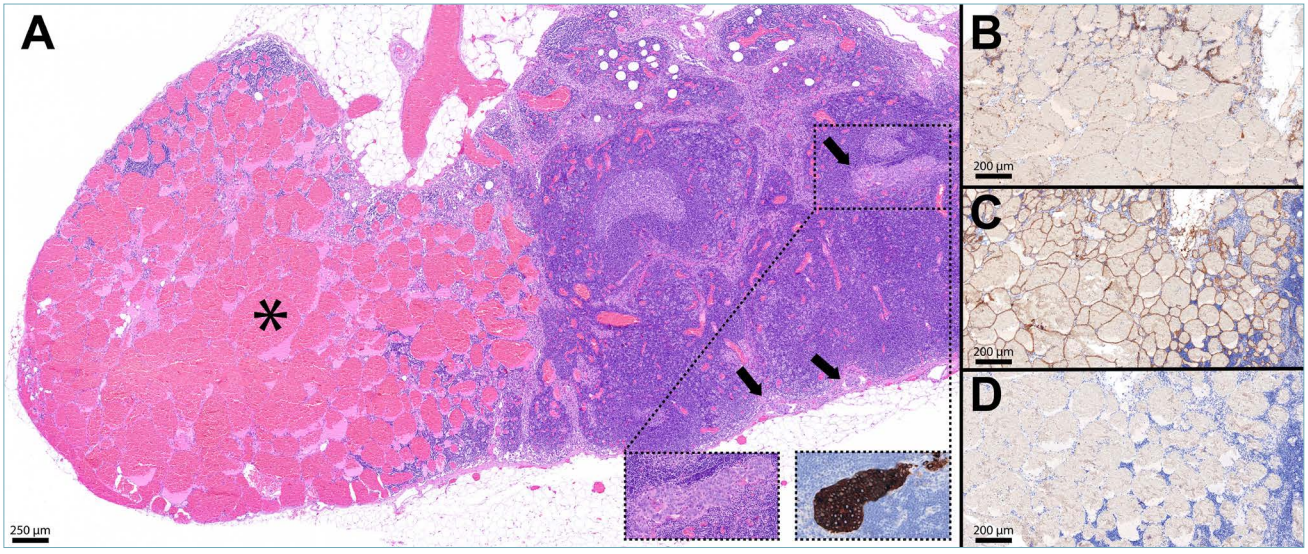

Figure 1. Primary solitary hemangioma and breast cancer metastasis coexist in a single axillary lymph node. Representative micrographs showing the thin-walled capillary hemangioma (star) occupying approximately 50% of the lymph node parenchyma along with multiple metastatic deposits from breast cancer (arrows) and neoplastic emboli inside of non-neoplastic lymph vessels, as also demonstrated by cytokeratin staining (A, hematoxylin and eosin, original magnification, 50x; and insets, hematoxylin, and eosin and original magnification, pan-cytokeratin, 200x). At the immunohistochemical analysis, the lesion was positive for both CD31 (B, original magnification, 50x) and CD34 (C, original magnification, 50x), while D2-40 (aka podoplanin) was negative (D, original magnification, 50x).

fined vascular proliferation was observed, measuring 0.4 cm in its largest dimension (Fig. 1). Morphologically, this lesion was characterized by an abundance of small-caliber, thin-walled capillaries that seamlessly replaced part of the lymph node parenchyma, echoing the morphology of capillary hemangioma. These vessels were lined by single-layered plump endothelial cells devoid of atypia. Immunohistochemical analysis revealed CD31 and CD34 positivity, while D2-40 was notably absent. The stromal composition of the periphery of the lesion was modestly fibrous with scarce neutrophilic infiltration. The metastatic deposits of breast cancer were constituted by multiple intraparenchymal and subcapsular foci, alongside a few metastatic emboli within subcapsular vessels (Fig. 1).

Discussion

To our knowledge, this is the first observation of two distinct neoplastic conditions of this nature (i.e. breast cancer metastasis and primary hemangioma) within the same lymph node. This finding raises several important considerations. Firstly, it further confirms the significance of thorough histopathological evaluation when assessing lymph nodes, particularly in the context of malignancies [19,20]. Furthermore, this case illustrates the importance of acknowledging the possibility of multiple concurrent neoplastic conditions from different lineages while examining lymph nodes. The relationship between primary lymph node hemangioma and metastatic breast cancer remains unclear, hinting that their co-occurrence might be a coincidence. This case stimulates discussions on the rarity of lymph node hemangioma and the importance of meticulously recording such cases in the literature to improve our knowledge on their histopathology. Notably, there exists a prior instance where Karaosmanoglu and co-authors reported encountering a hemangioma within an intrapancreatic lymph node [21]. However, a thorough examination of the iconography presented in the manuscript favors the interpretation of the lesion as an arteriovenous malformation. As more instances of lymph node hemangiomas are documented and incorporated into the medical literature, a more complete comprehension and description of these lesions should naturally evolve.

Other important considerations are related to the comprehensive evaluation of lymph nodes, the rare coexistence of different neoplastic conditions, the uncertain relationship between primary lymph node hemangioma and breast cancer metastasis, and diagnostic complexities. An area that remains to be addressed revolves around the possible biological interplay between hemangiomas and metastatic solid tumors within a single lymph node. Attracting questions include the underlying mechanisms that facilitate such a juxtaposition, the potential interdependencies between these entities, and the broader implications for diagnostic accuracy in the clinical practice. One possible biological linkage could involve the tumor-associated inflammasome, which may activate angiogenesis-related pathways [22]. In addition, oncogenes activation is known to trigger the 'angiogenic switch' through the upregulation of angiogenic growth factors [23]. In this context, the tumor necrosis factor-alpha (TNFα) and vascular endothelial growth factor-C (VEGF-C) might play a part [19,24].

Epilogue

In our short journey through the fascinating field of lymph node hemangiomas and their diagnostic intricacies, we remain indebted to the pioneering contributions of Professor Juan Rosai to the topic of rare vascular proliferations and histopathology at large [25,26]. The importance of delineating these rare entities is not confined to a mere academic curiosity but it carries direct implications for our daily practice as pathologists. In this context, Juan Rosai's Collection of Surgical Pathology Seminars is still an invaluable resource,

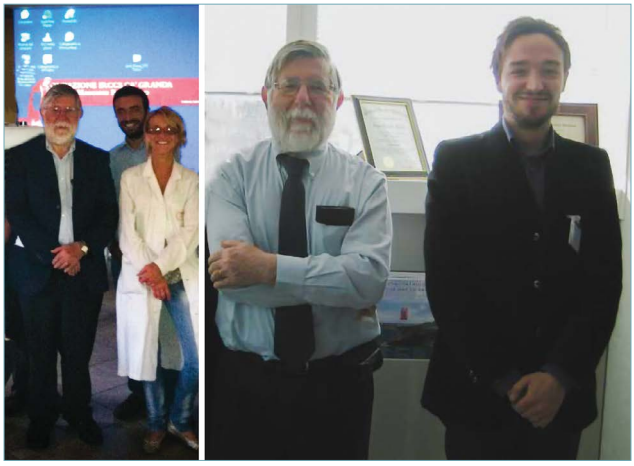

Figure 2. Captured moments of Juan Rosai (1940-2020) engaging with aspiring pathologists who participated in his weekly histological teaching sessions in Milan, Italy. The images feature three of the authors of this study (Nicola Fusco, Elena Guerini Rocco, and Fabio Pagni) during their tenure as pathology fellows, standing alongside the esteemed scholar. These photographs epitomize Juan Rosai's dedication to nurturing the future generation of pathologists (Photographs taken in Milan, 2012 circa).

Table I. Comprehensive overview of the 24 firmly established solitary primary lymph node hemangiomas available in the literature, alongside the present case. The cases are presented as either individual case reports or as part of the Prof. Juan Rosai case series (ref. 14). Cases of hemangiomatosis involving multiple anatomical sites, cases of contiguity infiltration from a non-lymph node primary hemangioma, publications in journals without rigorous peer-review standards (https://beallslist.net/, accessed in August 2023), works not published in English, or displaying dubious/low-quality iconography have been omitted from the present analysis.

Authors	Year	Gender	Age	Site of the lymph node	Histology	Size (mm)	Reason for primary surgery	Reference
Ivanova et al.	2023	Female	47	Axillary	Capillary	4	Breast cancer	Present case
Varugherese & Raji	2021	Female	67	Axillary	Capillary	20	Mass	4
Collins & Di Giuseppe	2019	Male	76	Axillary	Capillary	5[a]	T-cell lymphoma	5
Tessieras et al.	2019	Female	44	Axillary	Mixed	39	Mass	6
Sarris et al.	2018	Female	68	Axillary	Capillary	< 10[a]	Breast cancer	7
Terada	2013	Female	59	Iliac	Mixed	3	Endometrial cancer	8
Goto et al.	2011	Male	73	Hilar	Mixed	< 10[a]	Lung cancer	9
Pagni & Di Bella	2010	Female	68[b]	Iliac	Mixed	5[b]	Endometrial cancer	10
Reich et al.	2000	Female	11	Waldeyer ring	Mixed	17	Lipoma	11
Dellachà et al.	1999	Female	64	Iliac	Mixed	3	Ovarian cancer	12
Chan et al.	1992	Female	75	Axillary	Mixed	5	Breast cancer	13
		Female	61	Iliac	Mixed	3	Endometrial cancer	
		Male	Ad	Supraclavicular	Mixed	8	Mass	
		Female	74	Axillary	Mixed	3	Breast cancer	
		Female	38	Axillary	Mixed	2	Breast cancer	
		Female	21	Cervical (submental)	Lobular capillary	14	Mass	
		Male	14	Cervical (submental)	Lobular capillary	20	Mass	
		Female	51	Inguinal	Lobular capillary	10	Mass	
		Unknown	30	Inguinal	Cellular	15	Mass	
		Male	38	Cervical	Cellular	10	Mass	
		Male	20	Cervical	Cellular	20	Mass	
Har-El	1990	Female	17	Cervical	Mixed	35	Mass	14
Kasznica et al.	1989	Male	4	Inguinal	n/a	n/a	Mass	15
Goldstein & Bartal	1985	Male	52	Cervical	Cellular	20	Salivary gland tumor	16c
Lott & Davies	1983	Female	53	Axillary	Mixed	5	Breast cancer	17c

Legend: [a], size details not explicitly provided in the original manuscript but estimated through manual measurement of published figures by the Authors of this study; [b], supplementary information gathered by the original Authors (also co-Authors of this study) specifically for the present research and not included in the initial publication; [c], reclassified as hemangioma by Prof. Juan Rosai; Ad, adult (specific age information absent in the original manuscript and not derivable from published data); n/a data not available.

which is freely available to the pathology community at https://www.rosaicollection.org/. This comprehensive database of digital histological images, spanning decades of insights, is a testament to his enduring commitment to pathologists, pathology residents, and young medical students (Fig. 2).

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Conflicts of interest

The Authors declare no conflicts of interest.

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None.

Authors' contributions

All authors have significantly contributed to the research, analysis, and writing of this manuscript. Each author has reviewed and approved the final version for publication.

Ethical consideration

This case report is compliant with the local ethical guidelines.

References

1 Vascular Neoplasms of Lymph Nodes. In: Medeiros LJ, ed. Ioachim's Lymph Node Pathology. 5th Edition. Lippincott Williams & Wilkins 2022, pp 820-823.

2 Tsang WY, Chan JK, Dorfman RF, Rosai J. Vasoproliferative lesions of the lymph node. Pathol Annu. 1994;29 Pt 1:63-133.

3 Elgoweini M, Chetty R. Primary nodal hemangioma. Arch Pathol Lab Med 2012;136(1):110-112. https://doi.org/10.5858/arpa.2010-0687-RS Gupta, I. M. Haemangioma in a lymph node. Indian J Pathol Bacteriol 1964;55:110-111.

4 Varughese AA, Raji NL. Primary nodal hemangioma of axillary lymph node: A rare encounter. Indian J Pathol Microbiol. 2021;64(1):216-217. https://doi.org/10.4103/ijpm.Ijpm_979_19

5 Collins K, DiGiuseppe JA. Coincidental Lymphangioma and Hemangioma in a Single Lymph Node. Int J Surg Pathol 2019;27(5):527-528. https://doi.org/10.1177/1066896918810428

6 Tessieras J, Chenaye J, Senechaud C, et al. Intranodal capillary-cavernous hemangioma: Report of a very rare case. In SAGE Open Med Case Rep. 2019;7:2050313x19846710.

7 Sarris A, Matnei T, Candido F, et al. Primary lymph node hemangioma in a patient with invasive ductal carcinoma. Mastology. 2018;23:182-185. https://doi.org/10.29289/259453942018000025 8.

8 Terada T. Capillary cavernous hemangioma of the lymph node. Int J Clin Exp Pathol. 2013;6(6):1200-1201.

9 Goto T, Akanabe K, Maeshima A, et al. Hemangioma in a pulmonary hilar lymph node: case report. World J Surg Oncol. 2011;9:8. https://doi.org/10.1186/1477-7819-9-8

10 Pagni F, Di Bella C. Capillary cavernous hemangioma of lymph node. Int J Surg Pathol. 2010;18(5):338. https://doi.org/10.1177/1066896910375566

11 Reich RF, Moss S, Freedman PD. Intranodal hemangioma of the oral soft tissues: a case report of a rare entity with review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90(1):71-73. https://doi.org/10.1067/moe.2000.106303

12 Dellachà A, Fulcheri E, Campisi CA. lymph nodal capillary-cavernous hemangioma. Lymphology. 1999;32(3):123-125.

13 Chan JK, Frizzera G, Fletcher CD, et al. Primary vascular tumors of lymph nodes other than Kaposi's sarcoma. Analysis of 39 cases and delineation of two new entities. Am J Surg Pathol. 1992;16(4):335-350. https://doi.org/10.1097/00000478-199204000-00003

14 Har-El G, Heffner DK, Ruffy M. Haemangioma in a cervical lymph node. J Laryngol Otol. 1990;104(6):513-515. https://doi.org/10.1017/s0022215100113040

15 Kasznica J, Sideli RV, Collins MH. Lymph node hemangioma. Arch Pathol Lab Med. 1989;113(7):804-807.

16 Goldstein J, Bartal N. Hemangioendothelioma of the lymph node: a case report. J Surg Oncol. 1985;28(4):314-317. https://doi.org/10.1002/jso.2930280416

17 Lott, M. F, Davies, J. D. Lymph node hypervascularity: haemangiomatoid lesions and pan-nodal vasodilatation. J Pathol. 1983;140(3):209-219. https://doi.org/10.1002/path.1711400304

18 Maldonado D, Sturgeon A, Tarbox MB. Basal cell carcinoma arising within a longstanding hemangioma. Proc(Bayl Univ Med Cent). 2022;35(1):76-77. https://doi.org/10.1080/08998280.2021.196013 2

19 Shopov ST. A Collision between Cavernous-Capillary Hemangioma with Stromal Luteinization and Serous Cystadenoma. Folia Med (Plovdiv). 2020;62(4):851-855. https://doi.org/10.3897/folmed.62.e51551

20 Invernizzi M, Corti C, Lopez G, et al. Lymphovascular invasion and extranodal tumour extension are risk indicators of breast cancer related lymphoedema: an observational retrospective study with long-term follow-up. BMC cancer 2018;18(1):935. https://doi.org/10.1186/s12885-018-4851-2

21 Windsor GO, Bai H, Lourenco AP, et al. Application of artificial intelligence in predicting lymph node metastasis in breast cancer. Front Radiol 2023;3:928639. https://doi.org/10.3389/fradi.2023.928639

22 Zaveri S, Lillemoe HA, Teshome M, et al. Operative standards for sentinel lymph node biopsy and axillary lymphadenectomy for breast cancer: review of the American College of Surgeons commission on cancer standards 5.3 and 5.4. Surgery 2023;174(3):717-721. https://doi.org/10.1016/j.surg.2023.04.007

23 Karaosmanoglu AD, Arellano R, Baker G. Case report. Peripancreatic intranodal haemangioma mimicking pancreatic neuroendocrine tumour: imaging and pathological findings. Br J Radiol 2011;84(1008):e236-239. https://doi.org/10.1259/bjr/77657029

24 Mota de Oliveira M, Peterle GT, Monteiro da Silva Couto CV, et al. PAI-1 expression in intratumoral inflammatory infiltrate contributes to lymph node metastasis in oral cancer: a cross-sectional study. Ann Med Surg (Lond). 2021;65, 102303. https://doi.org/https://doi.org/10.1016/j.amsu.2021.102303.

25 Venetis K, Sajjadi E, Peccatori FA, et al. Immune plasticity in pregnancy-associated breast cancer tumorigenesis. Eur J Cancer Prev .2023. https://doi.org/10.1097/cej.0000000000000803

26 Dudley AC, Griffioen AW. Pathological angiogenesis: mechanisms and therapeutic strategies. Angiogenesis. 2023;26(3):313-347. https://doi.org/10.1007/s10456-023-09876-7.

27 Matanes E, Gotlieb WH. Pathophysiological and anatomical basis of lymphatic transit of cancer cells and role of the lymphatic system: a review of published literature. Chin Clin Oncol. 2021;10(2):14. https://doi.org/10.21037/cco-20-205

28 Sbaraglia M, Bellan E, Mentzel T, et al. The contribution of Juan Rosai to the pathology of soft tissue tumors. Pathologica 2021;113(5):396-409. https://doi.org/10.32074/1591-951x-551

29 Fellegara G, Tripodo C. A tribute to Juan Rosai. Pathologica 2021;113(5):302-304. https://doi.org/10.32074/1591-951x-535

30 Wick MR. Contributions of Dr. Juan Rosai to the pathology of cutaneous vascular proliferations: A review of selected lesions. Semin Diagn Pathol. 2016;33(5):284-293. https://doi.org/10.1053/j.semdp.2016.05.010