

CASE REPORT

Open Access



Sonographic changes in the thyroid gland after sclerotherapy with doxycycline can be mistaken for thyroid cancer

Steven Raeymaeckers^{1*} , Maurizio Tosi² , Bastiaan Sol³  and Johan De Mey¹ 

Abstract

Background The literature considers sclerotherapy to be a safe and effective treatment for benign thyroid cysts. No subsequent diagnostic problems have been reported as a complication. We report the occurrence of focal inflammation after said therapy, mimicking a thyroid malignancy.

Case presentation We report a case of a young male with a solitary strongly suspicious lesion in the thyroid. The patient had undergone prior sclerotherapy of a thyroid cyst with Doxycycline. The lesion appeared to be a focal area of inflammation and thus iatrogenic in nature. Systemic use of doxycycline is known to sometimes cause a non-immune chemical thyroiditis, dubbed as black thyroid due to the intense black discoloration of the thyroid. It might be that the instillation of doxycycline was responsible for a similar, more localized area of thyroiditis.

Conclusions For the work-up of a solitary suspicious thyroid lesion, the medical history of the patient should always be considered. In case of prior ipsilateral sclerotherapy, a reactive inflammatory response may mimic thyroid malignancy. A fine needle aspiration should be performed to exclude thyroid cancer. Treatment is not necessary; the process appears to be self-limiting as evidenced in the follow-up of this case.

Keywords Thyroid, Thyroid malignancy, TIRADS, Sclerotherapy, Doxycycline

Background

In case of benign thyroid cysts, percutaneous tetracycline instillation, ethanol sclerotherapy, or thyroid hormone suppression therapy can be performed [1]. Thyroid hormone suppression therapy is no longer advocated, as the effect of medication in volume reduction of a thyroid

nodule is uncertain and side-effects are to be expected [2]. Several sclerosants stimulate fibrous union of the tissue surfaces by inducing inflammation [3]. In our institution we opted to use doxycycline as a sclerosing agent, as it proved in our experience to be an effective and safe sclerosant for the treatment of seromas [3].

Doxycycline is an inexpensive drug and used to be readily available in its parenteral form. It is an antibiotic of the tetracycline family and its safety has been well established [4, 5]. Apart from its antibiotic properties, Doxycycline can be used as a sclerosant, for instance to treat pleurodesis of malignant effusions [6] or as treatment for lymphoceles [7] and lymphatic malformations [8, 9]. Parenteral forms of the drug are not available anymore in a number of countries (including the USA). It

*Correspondence:

Steven Raeymaeckers
steven.raeymaeckers@uzbrussel.be

¹Department of Radiology, Universitair ziekenhuis Brussel, Laarbeeklaan 101, 1090 Jette, Belgium

²Department of Anesthesiology, Universitair ziekenhuis Brussel, Laarbeeklaan 101, 1090 Jette, Belgium

³Department of Endocrinology, Universitair ziekenhuis Brussel, Laarbeeklaan 101, Jette 1090, Belgium



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

has since been established that treatment with a saline solution of the oral form of the drug is equally effective [10].

Case presentation

A 39-year-old male patient presented for routine follow up at our endocrine clinic. He had previously been treated for a recurrent bleeding cyst in the thyroid with sclerotherapy using doxycycline. Treatment had been performed because of progressive swallowing difficulties experienced by the patient, who refused surgical options. Initial aspiration of the cyst was inconclusive (Bethesda 1) but because of recurrence of the cyst, sclerotherapy was performed. One year after treatment, a mildly painful swelling of the right thyroid lobe was noted by the endocrinologist upon physical examination. No other abnormalities were present. Thyroid-stimulating hormone level was measured at 1.26 mIU/L (normal range 0.4 to 4.0 mIU/L), free T4 at 1.6 ng/dL (normal range 0.8 to 1.8 ng/dL). Free T3 was discretely elevated, measuring 4.3 pg/L (normal range 2.3–4.1 pg/mL).

Ultrasound revealed a large suspicious lesion in the right thyroid lobe. This lesion is illustrated in Fig. 1. The lesion appeared solid and markedly hypoechoic with irregular borders. It measured 14 mm in craniocaudal length. In the axial plane it measured 15 mm in antero-posterior length as opposed to 9 mm in laterolateral length, making this lesion taller than wide. It also seemed to contain some microcalcifications. Based on these criteria the lesion was graded as a TIRADS 5 lesion, necessitating a fine needle aspiration.

Upon examining the patient's medical history, we found evidence of the aforementioned sclerotherapy with Doxycycline. The patient had undergone this procedure one year earlier to treat a benign thyroid cyst in the right thyroid lobe (Fig. 2). Upon examination of the prior

ultrasound images, this cyst (although more voluminous in nature) appeared to be localized in the same region as the suspicious lesion.

Regardless, we decided to perform a fine needle aspiration to exclude an underlying thyroid malignancy. The fine needle aspiration sample was qualitative for diagnosis. The sample showed a relatively prominent amount of aqueous to slightly thickened colloid with some groups of follicle cells, as well as the presence of neutrophils, lymphocytes, and histiocytes. The sample was graded as a Bethesda 2 result. In this light, we considered the inflammation to be reactive following sclerotherapy and decided to follow up with ultrasound. Follow up ultrasound examinations showed no enlargement of the suspicious lesion, over the course of the next 4 years the lesion would even gradually reduce in size. In Fig. 3 we illustrate the follow-up ultrasound 4 years after the initial imaging, i.e. 5 years after sclerotherapy. On these images the lesion is found to be clearly smaller in size with a different morphology: the progressive formation of a macrocalcification and smooth borders of the lesion now more resemble a benign colloid nodule.

Discussion and conclusions

Ultrasound is the imaging modality of choice for the evaluation of the thyroid and the risk stratification/follow up of thyroid nodules. Many different proposals of a Thyroid Imaging Reporting and Data System (TIRADS) have been described in the literature. For the description of thyroid nodules in our hospital, we adhere to the system as proposed by Kwak et al. [11] Regardless of the TIRADS system used, several described sonographic features are nearly universal. Lesions that are mainly solid, hypoechoic or even markedly hypoechoic are more suspicious than lesions that are mixed or predominantly cystic. Lesion contours, taller-than-wide aspect and

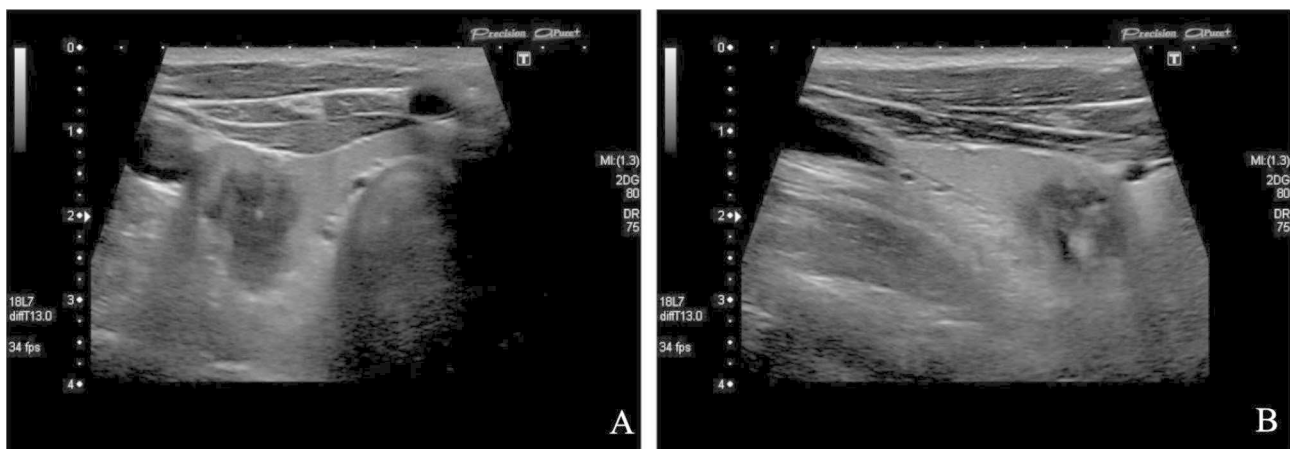


Fig. 1 Ultrasound of the thyroid gland

A (left): Axial plane. B (right) sagittal plane. Lesion in the lower part of the thyroid. The lesion is solid, hypoechoic with irregular borders. The lesion is also taller than wide and seems to contain some microcalcifications



Fig. 2 Ultrasound of the thyroid gland
Ultrasound prior to sclerotherapy, one year earlier. Note the large bleeding cyst in the right thyroid lobe

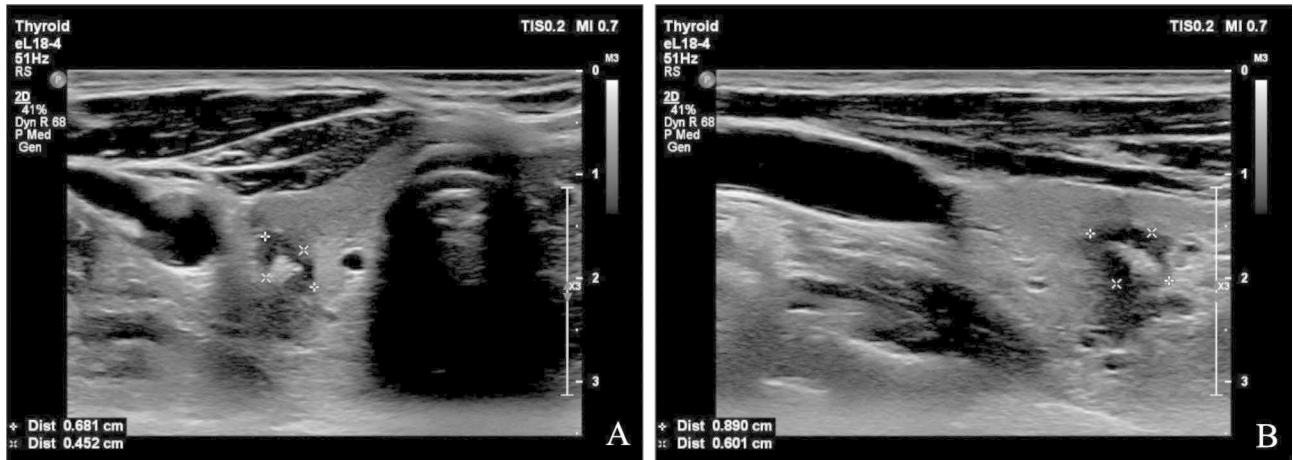


Fig. 3 Ultrasound of the thyroid gland
A (left): Axial plane. B (right) sagittal plane. Check-up ultrasound, 4 years later. The lesion is clearly smaller in size and with a different morphology: progressive formation of a macrocalcification and now smooth borders

microcalcifications are other remaining factors that should be considered.

The literature considers sclerotherapy to be a safe and effective treatment for benign thyroid cysts. Sclerotherapy is almost exclusively performed by percutaneous ethanol injection (PEI), the safety of this procedure has been well established since the introduction of the technique in 1990 by Livraghi et al. [12] These authors followed 101

patients over the course of 4 years to evaluate the long-term efficacy of their proposed treatment.

A large clinical trial on the use of PEI was subsequently conducted by Lee et al. [13] and included 654 patients. Not only did these authors opt to treat thyroid cysts, but they treated solid nodules as well. Complete response, partial response and no response were found to be 17.2%, 71.7%, 11.1% in solid nodules as compared to 19.0%, 60.4%, 20.6% for complex cysts, respectively.

Minimally invasive treatment of symptomatic thyroid nodules has since become commonplace. Therefore, the Task Force Committee of the Korean Society of Thyroid Radiology initiated a consensus statement providing recommendations for the role of PEI in the management of symptomatic thyroid nodules [14]. These guidelines consider different known complications of sclerotherapy, such as localized pain, hematoma, facial flushing, drunken sense, hoarseness, dyspnea, and temporary hyperthyroidism. In malignant cases, tumor implantation can occur as a very rare complication that can occur months to years after PEI [15].

The patient described in this report was also treated for a benign thyroid cyst, with doxycycline as a sclerosing agent. None of the aforementioned complications was present in our case, however a routine follow-up one year later found a large suspicious lesion present in the treated region of the thyroid. Considering the timeframe, the localization of this lesion and the inflammatory cells found in the fine needle aspirate, it seems logical to consider a link to the prior treatment. No other case can be found in the literature in which a diagnostic problem arose after PEI treatment of a thyroid cyst, nor in those few studies where different sclerosing agents were used.

It could be we witnessed a common but underreported effect of thyroid sclerotherapy in general, due to small patient groups and lack of follow-up. If this is the case, patients who have undergone sclerotherapy might be at risk of false-positively being diagnosed with thyroid malignancy if the relevant medical history is not considered. The aforementioned study by Lee et al. [13] however included 654 patients who were followed up for 36 months after PEI treatment and did not report on any such complications.

As sclerotherapy is usually performed with ethanol, it can then be suggested that doxycycline is specifically the agent to blame in this case. Systemic use of doxycycline is known to sometimes cause a non-immune chemical thyroiditis [16], dubbed as black thyroid due to the intense black discoloration of the thyroid [17]. It might be that the instillation of doxycycline was responsible for a similar, more localized area of thyroiditis.

In conclusion we would suggest that for the work-up of a solitary suspicious thyroid lesion, the medical history of the patient should always be considered. In case of antecedents of ipsilateral sclerotherapy, a reactive inflammatory response may mimic thyroid malignancy. In this specific case Doxycycline was responsible, an effect that may specifically be explained by the occurrence of non-immune chemical thyroiditis. It is not known if other sclerosants may elicit the same effect, however this complication was not reported in large follow-up studies that use ethanol as sclerosing agent. It could however be that these inflammatory changes post sclerotherapy have

not been reported as this may be thought of by different authors as a normal process. Fine needle aspiration should be performed to exclude thyroid cancer. Treatment is not necessary; the affliction appears self-limiting as evidenced in the follow-up of this case.

List of abbreviations

TIRADS	Thyroid Imaging Reporting and Data System
PEI	Percutaneous ethanol injection

Acknowledgements

Not applicable.

Authors' contributions

SR wrote the text and prepared the figures. BS revised the text. MT proofread the text and provided assistance in the production process. JD supervised the text.

Funding

Not applicable.

Data Availability

Not applicable.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Patient consent for publication of the ultrasound images was obtained.

Received: 16 January 2022 / Accepted: 3 August 2023

Published online: 17 August 2023

References

1. Hahn SY, Shin JH, Na DG, et al. Ethanol ablation of the thyroid nodules: 2018 Consensus Statement by the Korean Society of Thyroid Radiology. *Korean J Radiol.* 2019;20(4):609–20.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid Cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid Cancer. *Thyroid.* 2016;26(1):1–133.
3. Sood A, Kotamarti VS, Therattil PJ, Lee ES. Sclerotherapy for the management of Seromas: a systematic review. *Eplasty.* 2017;17:e25.
4. Shergill A, John P, Amaral JG. Doxycycline sclerotherapy in children with lymphatic malformations: outcomes, complications and clinical efficacy. *Pediatr Radiol.* 2012;42(9):1080–8.
5. Cho YS, Lee HK, Ahn IM, Lim SM, Kim DH, Choi CG, Suh DC. Sonographically guided ethanol sclerotherapy for benign thyroid cysts: results in 22 patients. *AJR Am J Roentgenol.* 2000;174(1):213–6.
6. Heffner JE1, Standerfer RJ, Torstveit J, Unruh L. Clinical efficacy of doxycycline for pleurodesis. *Chest.* 1994;105(6):1743–7.
7. Caliendo MV, Lee DE, Queiroz R, Waldman DL. Sclerotherapy with use of doxycycline after percutaneous drainage of postoperative lymphoceles. *J Vasc Interv Radiol.* 2001;12(1):73–7.
8. Nehra D, Jacobson L, Barnes P, Mallory B, Albanese CT, Sylvester KG. Doxycycline sclerotherapy as primary treatment of head and neck lymphatic malformations in children. *J Pediatr Surg.* 2008;43(3):451–60.

9. Thomas DM, Wieck MM, Grant CN, Dossa A, Nowicki D, Stanley P, Zeinati C, Howell LK, Anselmo DM. Doxycycline sclerotherapy is Superior in the treatment of Pediatric Lymphatic Malformations. *J Vasc Interv Radiol*. 2016;27(12):1846–56.
10. Bilaceroglu S, Guo Y, Hawthorne ML, Zhu Z, Stathopoulos GT, Lane KB, Light RW. Oral forms of tetracycline and doxycycline are effective in producing pleurodesis. *Chest*. 2005;128(5):3750–6.
11. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, Jung HK, Choi JS, Kim BM, Kim EK. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. *Radiology*. 2011;260(3):892–9.
12. Livraghi T, Paracchi A, Ferrari C, Reschini E, Nacchi RM, Bonifaino A. The treatment of autonomous thyroid nodules with percutaneous ethanol injection: 4 year experience. *Radiology*. 1994;190:529–33.
13. Lee SJ, Ahn IM. Effectiveness of percutaneous ethanol injection therapy in benign nodular and cystic thyroid diseases: long-term follow-up experience. *Endocr J*. 2005;52(4):455–62.
14. Hahn SY, Shin JH, Na DG, Ha EJ, Ahn HS, Lim HK, Lee JH, Park JS, Kim JH, Sung JY, Lee JH, Baek JH, Yoon JH, Sim JS, Lee KH, Baek SM, Jung SL, Kim YK, Choi YJ. Korean society of thyroid radiology (KSThR); korean society of Radiology. Ethanol ablation of the thyroid nodules: 2018 Consensus Statement by the korean society of thyroid Radiology. *Korean J Radiol*. 2019;20(4):609–20.
15. Rodríguez-Lomba E, Molina-López I, Parra-Blanco V, Suárez-Fernández R, Ciudad-Blanco C. Cutaneous implantation of papillary thyroid carcinoma secondary to percutaneous ethanol injection into nodal metastasis. *J Eur Acad Dermatol Venereol*. 2018;32(1):e11–3.
16. Pollock AJ, Seibert T, Allen DB. Severe and persistent thyroid dysfunction Associated with tetracycline-antibiotic treatment in Youth. *J Pediatr*. 2016;173:232–4.
17. Miller BT, Lewis C, Bentz BG. Black thyroid resulting from short-term doxycycline use: case report, review of the literature, and discussion of implications. *Head Neck*. 2006;28(4):373–7.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.