

Peer Review File

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Reviewer comments

Reviewer A

Haught E. and Bendre S. reported a case of acute suppurative thyroiditis caused by bacterial infection through pyriform sinus fistula. Although this condition might be rather rare especially in the USA and Europe, it is very important clinically, since it is an endocrine emergency requiring prompt and accurate diagnosis and appropriate treatments. The present report is typical and very educational, thus should be very important.

In order to improve the report, the Reviewer would like to suggest the followings in the order of the appearance in the manuscript:

Comment 1: Throughout the manuscript, “hyperthyroidism” should be replaced with “thyrotoxicosis”. Obviously, the present patient had “destructive thyrotoxicosis”, but not hyperthyroidism.

Reply 1: I agree.

Changes in text: We changed all “hyperthyroidism” to “thyrotoxicosis.”

Comment 2: Line 47: The Reviewer would like to know the values of FT4 and TSH, if editorial limitation allows.

Reply 2: I agree

Changes in text: Added to line 27: FT4 was high at 7.0 ng/dL and TSH was low at 0.04 uU/mL.

Comment 3: Line 48: the right lobe: Since about 95% of pyriform sinus fistula are on the left side, the Reviewer thinks a short comment on the laterality be appropriate.

Reply 3: I agree, and think a comment on laterality is appropriate in the discussion.

Changes in text: I added this to line 71: Interestingly, the majority of pyriform sinus fistulas occur on the left; however, our patient’s fistula was on the right.

Comment 4: Lines 51-52. The authors prescribed methimazole and prednisone, probably with an erroneous diagnosis of subacute thyroiditis. The Reviewer admits this can occur and actually saw several patients prescribed glucocorticoid by primary care physicians, resulting in aggravation of the inflammation. Methimazole is of no use, actually contraindicated for the present patient, since the present patient had destructive thyrotoxicosis, but not hyperthyroidism. This should be clearly mentioned in Discussion.

Reply 4: I agree

Changes in text: I added this to line 81: Our patient was first prescribed methimazole and prednisone due to the inaccurate diagnosis of hyperthyroidism. Methimazole is contraindicated for a patient with destructive thyrotoxicosis due to potential aggravation of inflammation.

Comment 5: Line 55. Direct laryngoscopy: Was the procedure performed with a flexible fiberscope or a rigid laryngoscope? Was it done under general anesthesia? These should be described.

Reply 5: Flexible; awake

Changes in text: Added to line 41: an awake flexible fiberscope direct laryngoscopy

Comment 6: Line 56. Purulent fluid was seen entering the sinus when external pressure was applied to the abscess.: This might be coming out.

Reply 6: I am confused by the comment; please advise. Thank you!

Comment 7: Lines 61-62: A right hemithyroidectomy was performed.: The Reviewer thinks simple thyroidectomy is not sufficient to prevent recurrence of the inflammation. The part of the fistula penetrating the laryngeal framework around the cricothyroid joint should be resected.

Reply 7: The reviewer makes a valid point. I believe only a hemithyroidectomy was performed, however.

Comment 8: Discussion, lines 76-81. The authors discussed on the embryology of the pyriform sinus fistula and suggested the third or fourth pharyngeal pouch origin citing several papers. However, these statements are based on several dissertations with quotations in quotations and are not based on the original findings and these hypotheses do not explain well on the embryology of the fistula. The Reviewer thinks the following is the most likely explanation for the fistula embryology: In embryonic period, the ultimobranchial body arises in the most caudal part of the fourth pharyngeal pouch, migrates caudally to join the developing thyroid, and disseminates into it to become C cells. Based on histological findings especially on the distribution of C cells and the anatomical relationships of the fistula with the major anatomical structures in the neck, Miyauchi et al. suggested that this fistula being a remnant of the pharyngeal mucosa that was brought together with the migration of the C cells (1). According to their hypothesis, the fistula traces the route of the migration of C cells from their embryonic origin. This hypothesis clearly explains the close relation of the fistula with the thyroid.

Reference:

1) Miyauchi A, Matsuzuka F, Kuma K, Katayama S: Piriform sinus fistula and the ultimobranchial body. *Histopathology* 20: 221-27, 1992.

Reply 8: Thank you for this information.

Changes in the text: I replaced this citation "Rosenfeld RM, Biller HF. Fourth branchial pouch sinus: diagnosis and treatment. *Otolaryngol Head Neck Surg.* 1991;105(1):44-50." with the citation you suggested (miyauchi). I deleted the description I had and added this to line 58: Miyauchi et al. hypothesizes that pyriform sinus fistulas are a remnant of pharyngeal mucosa that was created with migration of C cells. The tract is formed from the migration pathway the ultimobranchial body takes caudally from the fourth pharyngeal pouch to join the developing thyroid and become C cells.

Reviewer B

Haught and Bendre describe the case of a 14-year-old who presents with symptoms of hyperthyroidism and pressure symptoms from a thyroid abscess. The take away message from their case is to consider AST in patients presenting with thyroiditis with negative antibodies and to look for pyriform sinus fistula if this is the case.

I have a few comments below to improve the manuscript:

Comment 1: Title - 'Thyroid abscess in NF1 due to a pyriform sinus' - needs to include fistula at the end as it is not due to pyriform sinus

Reply 1: Thank you; I must've overlooked this

Changes in text: I added "fistula" to the end of the short title on the title page

Comment 2: In both the abstract and introduction they say that pyriform sinus fistulas are being 'increasingly recognized' however it is a known cause of AST.

Reply 2: I agree.

Changes in text: I deleted "increasingly" on line 2 and line 15

Comment 3: Given the main learning point in this case is that in hyperthyroidism you should consider AST, FT4 and TSH levels should be included as well as baseline bloods including WCC/CRP/ESR to let the reader know how unwell/well this patient may have been

Reply 3: I agree.

WBC= 17.2 K/cu mm

Crp and esr was unfortunately not completed

Changes in text: Added to line 27: FT4 was high at 7.0 ng/dL and TSH was low at 0.04 uU/mL. Added to line 38: the white blood cell count was 17.2 K/cu mm,

Comment 4: What were the findings of US/CT? Was CT contrast/non-contrast? Was there a suggestion of an abscess? Were there any features to suggest AST? (Refer the authors to Masuoka et al 2011)

Reply 4: Ultrasound and CT neck showed an enlarged right thyroid lobe measuring 5.2 x 2.4 x 2.5cm with a heterogeneous nodular region.

Ultrasound: heterogenous echogenicity of entire right lobe; differential including focal thyroiditis or hemorrhage of the right thyroid gland

CT: noncontract; heterogenous mass either originating from or invading into right thyroid lobe; differential is neoplastic.

-nothing appeared to look like an abscess on these scans.

Changes in text: Added to line 29: Ultrasound and noncontrast CT neck showed an enlarged right thyroid lobe measuring 5.2 x 2.4 x 2.5cm with a heterogeneous nodular region. There was no evidence of a thyroid abscess on the scans. The differential diagnosis at the time appeared to be focal thyroiditis, hemorrhage of the right thyroid gland, or a neoplasm.

Comment 5: Treatment included methimazole, prednisolone and Augmentin. What was the presumed diagnosis or differential diagnosis at this stage? What was the patient being treated

for?

Reply 5: The presumed diagnosis was subacute thyroiditis. The augmentin was added due to the left shift before doing a laryngoscopy to look further at the anatomy.

Changes in text: I added: “what was presumed to be subacute thyroiditis” to line 81.

Comment 6: What was the time frame to FNA? Was this inpatient/outpatient management? Why was an FNA performed at this stage? It would be good to clarify the clinical history better to elucidate why this particular patient with thyroiditis was different from others so other doctors can appreciate when they would think about this diagnosis.

Reply 6: The FNA was performed because of the size of the nodular region (5.2 x 2.4 x 2.5cm), due to the results of the radioactive iodine uptake (cold nodule), and lack of information on the scans.

Changes in text: Added to line 39: Fine needle aspiration (FNA) was performed due to the size of the nodular region and the results of the radioactive iodine uptake. The FNA was an outpatient procedure performed shortly after the results of the CT and RAI were received and revealed a thyroid abscess.

Comment 7: Line 55 suggests that the direct laryngoscopy was performed to remove the thyroid abscess. Was it not performed to see if they had a pyriform sinus fistula?

Reply 7: My wording was wrong; you are correct

Changes in text: Changed in line 41: A pyriform sinus fistula was discovered during direct laryngoscopy to further investigate the anatomy.

Comment 8: Line 63 - TSH level should be provided

Reply 8: I agree

Changes in text: Added to line 51: rising TSH of 7.32 uIU/mL.

Comment 9: Line 74-75 - what are the references for this? I am not aware of thyroglossal duct remnant or patent foramen cecum as a cause of AST.

Reply 9: I searched through some articles and cannot find where I found that.

Changes in text: I deleted “thyroglossal duct remnant, and patent foramen cecum”

Comment 10: Lines 82-89 discusses how common hyperthyroidism is in AST, then talks about how pyriform sinus fistulas present then goes back to discuss how AST presents. This is quite confusing. I would suggest discussing AST first in a paragraph and pyriform sinus fistula presentation can be discussed later as they are separate conditions that can co-exist.

Reply 10: I agree. I rearranged the text.

Changes in text: Starting on line 71 now reads:

Presentation of an infected thyroid from a pyriform sinus fistula can vary, but most patients are euthyroid. A retrospective study that evaluated 48 cases of pyriform sinus fistulas revealed 62.5% of the cases presented as a neck abscess while some presented with dyspnea, acute suppurative thyroiditis, or a thyroid nodule [4].

Acute suppurative thyroiditis can present as anterior neck swelling, pain, fever, and increased WBC count [5]. Hyperthyroidism, as reported in a review by Lafontaine et al, has been reported

in up to 42% of case reports in patients with acute suppurative thyroiditis [5]. Our patient presented with acute suppurative thyroiditis, thyroid nodule with pressure symptoms, along with hyperthyroid symptoms. Interestingly, the majority of pyriform sinus fistulas occur on the left; however, our patient's fistula was on the right.

Comment 11: Hyperthyroidism is more common than 12%, as described in recent review by Lafontaine et al, reported in up to 42% of case reports, which is why their learning point of considering AST in hyperthyroidism is important

Reply 11: I agree.

Changes in text: I deleted "Although, a review of suppurative thyroiditis showed that there have been exceptions including 12% of patients with thyrotoxicosis and 17% with hypothyroidism [3]." And deleted this citation because it is likely outdated.

I added this to line 77: Hyperthyroidism, as reported in a review by Lafontaine et al, has been reported in up to 42% of case reports in patients with acute suppurative thyroiditis [5].

I added Lafontaine's citation.

Comment 12: Line 96 - 'treatment must include antibiotics to control the infection as well as incision and drainage if there is an abscess' - This is misleading. There is increasing evidence that needle aspiration is an acceptable therapy in selected patients (both in Paes et al and Lafontaine et al).

Reply 12: I will fix

Changes in text: I changed to "Incision and drainage or needle aspiration are acceptable therapies for abscesses." Line 103

Comment 13: Both in the conclusion and in the abstract, they state that thyroiditis 'in the absence of antibodies' should prompt investigation into infection however I am unaware of any studies looking at presence of antibodies in AST v/s other causes of thyroiditis in helping to differentiate between causes. This is not discussed in their discussion and the antibody status of their case is also not stated.

Reply 13: On line 29 we state: "Thyroglobulin and thyroid peroxidase antibodies were negative." For our patient. I agree with you in that I have not seen any studies looking at presence of antibodies in AST.

Changes in text: Line 6 and line 126, I deleted "in the absence of antibodies"

Comment 14: Lines 102-106 - I think it is important to highlight that there is mortality associated with this condition which is why it is crucial that this is managed early and pyriform sinus fistula should be excluded to prevent recurrence.

Reply: thank you; I used lafontaines text to reference this

Changes in text: I added "According to the Lafontaine et al review, patients with acute suppurative thyroiditis had 7.8% mortality [5]" to line 112.