Reviewer's report

Title: Gorlin syndrome associated with small bowel carcinoma and neuroleiomyomatosis of the gastrointestinal tract: Case report and review of literature

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Reviewer: Mariana Cajaiba

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The manuscript has undergone significant improvement after the authors re-drafted it into a more comprehensive format. The majority of comments/questions have been satisfactorily answered.

The clinical report is interesting and complete, and deserves consideration for publication. From a pathologist standpoint, however, I believe the intestinal lesion referred to as neuroleiomyomatosis still lacks further characterization to be defined as a new/rare lesion. I would recommend the use of descriptive terms (such as mesenchymal proliferation with neural and smooth muscle components, for example), instead of labeling it as a lesion that has not been fully characterized. Based solely on the morphological description provided by the authors (as there is little described in the literature), I would find it extremely difficult to use this diagnosis on my pathologist practice when faced with a similar lesion. If they still wish to use this term, further characterization, including more detailed morphological documentation of this lesion, should be considered.

Some questions about the mesenchymal lesion:

1. Page 4, lines 7-11: "Antibodies against neurofilament proved the presence of neurons, indicating the proliferation of both, Schwann cells and neuronal cells within the nodules. No expression of CD117 or CD34 was detectable in the spindle cell tumors arguing against the presence of a gastrointestinal stromal tumor (GIST). Staining with Cathepsin D, Synaptophysin and Chromogranin A revealed only single positive cells, excluding ganglieneuromatosis."

   These sentences are contradictory. First, it is said:’ Antigodies against neurofilament proved the presence of neurons, indicating the proliferation of both, Schwann cells and neuronal cells within the nodules…", and then "Staining with Cathepsin D, Synaptophysin and Chromogranin A revealed only single positive cells…".

   So, was there or not a neuronal component? This changes the diagnostic approach in this case.

2. Could the smooth muscle proliferation (documented with the desmin stain) represent a reactive process to a neural neoplasm, rather than a neoplastic component?
3. The second paragraph of page 6 gives a very a nice discussion about the pathogenic effects of this mutation and the resulting lesion, without labeling it.

Some other points are still worth to be considered:

1. It would be interesting to know if the reported PATCH mutation has been previously described or documented in a mutation database; if yes, was it associated with any particular phenotype?

2. Page 3, last paragraph: "After sectioning, the nodules were located in the mucosa and submucosa of the small intestine with a maximum node diameter of 3.5 cm. Microscopic examination revealed numerous nodules (>100) that centred at the muscularis mucosa and extended into the submucosa and the lamina propria of the mucosa."

   It is hard to imagine how microscopic examination of the bowel specimen disclosed the presence of >100 nodules, as extensive histological sampling would be needed for that; wasn’t it a gross (macroscopic) finding instead, with representative sampling of some of these nodules?

3. Same sentence as above: "...maximum node diameter of 3.5 cm...". Use the term nodule instead of node, as the latter suggests the presence of lymph nodes.

4. Page 7, lines 1-3 and 7-10: “Has the small bowel carcinoma derived from the neuroleiomyomatosis, or are both features not directly associated with each other but nevertheless both pathogenetically linked to the PTCH stop codon mutation?” and “If the adenocarcinoma in our patient is indeed pathogenetically connected with the neuroleiomyomatosis, the malignant potential of the later is probably to low to raise a red flag in a syndrome this rare.”

   It would be really difficult to explain the pathogenesis of an epithelial neoplasm (adenocarcinoma) arising from a mesenchymal neoplasm.

5. There are still minor spelling errors, which can be probably fixed by the publisher during review of manuscript proofs.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.