Reviewer's report

Title: Severe Paraneoplastic Hypoglycemia in a Gastrointestinal Stromal Tumor with an Exon 9 Mutation: A Case Report

Version: 1 Date: 2 November 2006

Reviewer: John H Donohue

Reviewer's report:

General: This is a case report of severe hypoglycemia in a GIST patient, who responded well to tumor debulking. The tumor had a rare exon 9 mutation and the authors imply that this genotype may be the cause of the elevated IGF II levels and hyperglycemia. This is a rare complication of this form of malignancy and the patient did well in the short term.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The text and Figure 1 state that the tumor was "multicentric". Were there multiple separate tumors, implying peritoneal seeding, or was the this a single multilobulated tumor?
2. What was the organ of origin (i.e. stomach, small bowel or what)?
3. In the abstract the authors state that imatinib would be an alternate treatment for hypoglycemia in a GIST patient. Do they have data to support this statement?
4. Do the authors' have a more definitive reason or hypothesis to suspect that this particular exon 9 mutation induced the patient's hypoglycemia other than both occurred in this patient? If not they should not stress the potential link as strongly.
5. Most GIST tumors are discovered because of symptoms or clinical signs, rather than asymptomatic incidental findings as stated in the Background section.
6. Was the resection complete or was residual tumor left behind (i.e. R0, R1, or R2)?
7. What other structure(s) were resected with the neoplasm?
8. Has the patient been treated with a postoperative tyrosine kinase inhibitor?
9. Were any specific mutations sought in the IGF II gene, or is IGF II expression affected by KIT activity (potential mechanisms for IGF II product overexpression)?
10. The authors state that radio frequency ablation might be an alternate treatment for tumor hyperglycemia. Is there potential for transient worsening of the hypoglycemia with a bolus of IGF II release from necrotic tumor?
11. The use of steroids and growth hormone as treatment for tumor-induced hyperglycemia is mentioned in the abstract and conclusions but not in the body of the paper. This should be included in the discussion.
12. The authors should clarify the sequencing results shown in Figure 2.
13. The IHC staining in Figure 3 is not readily seen in my copies of the photomicrographs.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Is KIT the gene product and c-kit the actual gene mutated in most GIST tumors rather than both being synonyms?
2. The Figure 1 a/b caption should be revised to read "... oral and intravenous contrast..."

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest
Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests.