Definitive surgical treatment of osteomalacia induced by skull base tumor and determination of the half-life of serum fibroblast growth factor 23

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Abstract. Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome often associated with fibroblast growth factor 23 (FGF23)-producing tumors such as phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT) affecting the bone and soft tissue. We experienced a patient with progressive bone and muscle pain due to FGF23-related TIO. Venous sampling had strongly suggested the anterior skull base as a source of FGF23, which led to the discovery of a small tumor in the ethmoid sinus extending intracranially. Radical surgical resection confirmed the histological diagnosis of PMTMCT with FGF23 immunopositivity and achieved durable tumor control with complete resolution of symptoms. We serially measured serum FGF23 level before, during and after surgery and analyzed the data to determine the half-life of FGF23. Serum FGF23 level sharply declined as early as 20 minutes after en bloc tumor resection and completely normalized after surgery. The half-life of FGF23 was calculated to be approximately 18.5 minutes using single phase exponential decay model as well as semilog transformation formula. Serial measurements of serum FGF23 level can potentially declare “complete” resection of a FGF23-producing tumor and total cure of TIO; in this regard, development of its intraoperative measurement would be helpful in the management of this endocrine tumor.

Key words: Fibroblast growth factor 23, Half-Life, Phosphaturic mesenchymal tumor, Tumor induced osteomalacia, Intraoperative measurement

Materials and Methods

Patient presentation

The patient is a 38-year-old woman who initially presented with progressive bone and muscle pain at the age of 29, and was found to have elevated serum FGF23 level. Subsequent development of olfactory disturbance led to the discovery of a small tumor in the ethmoid sinus, for which she underwent transnasal endoscopic surgery at the age of 36. Histological diagnosis was PMTMCT with immunopositivity for FGF23 (Fig. 1). Since intracranial extension through the cribriform plate prevented complete resection, serum FGF23 level did not normalize nor did her
symptoms recover fully. Rather, olfactory disturbance deteriorated further, and follow-up MRI scans showed progression of the remnant tumor with more intracranial involvement (Fig. 2). Laboratory findings included low serum phosphate level (1.3 mg/dL (reference, 2.5-4.5 mg/dL)) and high FGF23 level (120 pg/mL (10-50 pg/mL)). Renal function was normal (serum creatinine 0.45 mg/dL (0.4-0.9 mg/dL), estimated GFR 120.9 mL/min/1.73m² (90 mL/min/1.73m²)) and it remained normal throughout the subsequent course of treatment. Serum calcium level was 9.1 mg/dL (8.4-9.7 mg/dL), iron level was 73 µg/dL (0.4-0.9 mg/dL), and 1,25-dihydroxyvitamin D level was 20.5 pg/mL (20-60 pg/mL). Venous sampling revealed that FGF23 level was elevated especially in several veins of the head and neck, strongly suggesting the anterior skull base tumor as a source of FGF23 (Fig. 3). Therefore, she underwent craniotomy for curative resection. The tumor as well as the invaded ethmoid bone were removed en bloc, and large defect at the skull base was repaired with a pedicle subgaleal flap. The histology of the resected tumor looked identical to that of the initial nasal tumor, and hence the diagnosis of PMTMCT (Fig. 1).

At the 25-month follow-up, muscle and bone pain had completely resolved. Serum phosphate level recovered to the normal level without medications. Serum FGF23 level remained normal and MRI scan showed no recurrent tumor.

Measurement of serum FGF23 level and assessment of half-life

Intraoperatively, we sequentially collected blood samples from right medial cubital vein for the analysis of serum FGF23 level before tumor resection as well as 20 and 60 minutes after resection. Postoperatively, we continued blood sampling right after surgery and 1, 2, 4 days, 2 weeks, and 1 month after. Serum FGF23 level...
The half-life of serum FGF23 was measured by intact assay (Kainos, Tokyo, Japan) [5]. The half-life of FGF23 was determined using two mathematical methods: single phase exponential decay model and semilog transformation formula. The software used was Prism 6 (GraphPad Software, San Diego CA, USA) for the former and Excel 2010 (Microsoft, Redmond WA, USA) for the latter.

**Results**

A sharp decline of serum FGF23 level was observed 20 minutes after tumor removal, and it normalized postoperatively (Fig. 4a). FGF23 levels at 2 weeks and 1 month after surgery were likely due to the inherent secretion of FGF23, which had been long suppressed by the FGF-producing tumor. Serum phosphate level normalized one week after surgery. A single phase exponential decay model calculated the half-life of FGF23 to be 18.4 minutes (Fig. 4b). The half-life was also calculated with semilog transformation formula. FGF23 levels at different time points were plotted to a logarithmic graph and the following exponential approximation line was obtained: 

\[ y = 54.823e^{-0.035x} \]  

\( e \) base of natural logarithm. The half-life of FGF23 was calculated as \( x \) when \( y \) was 50% of the level of preoperative FGF23 level (56.7 pg/mL) (Fig. 4c). It was 18.9 minutes and consistent with the single phase exponential decay model. Therefore, the half-life of FGF23 was determined to be approximately 18.5 minutes.

**Discussion**

The cure of a paraneoplastic syndrome such as TIO is only possible when a causative tumor is totally removed from the body, usually by means of complete surgical resection. Intracranial FGF23-producing PMTMCT is extremely rare and, to the best of our knowledge, only 17 cases have been reported in the literature to date (Table 1) [6-20]. It tends to affect sterically complicated areas such as the anterior skull base. An aggressive resection putting margins to the tumor warrants “total” removal most confidently, but it requires extensive repair of the skull base. In case of recurrence, reoperation will have an even higher degree of difficulty given expected adhesion and lack of a pedicle flap available for repair. These underscore the need for establishing a reliable, and desirably real-time assessment of the extent of resection.

Serum FGF23 measurement has an important role in the follow-up management of TIO. Assessment of the extent of resection based on postoperative MRI scan is often difficult because of postoperative change, while the postoperative sequential measurements of serum FGF23 level can suggest the residual tumor if the level fails to get down to normal. In such a case, early reoperation with vigorous search for the residual would be recommended. During the follow-up, increased FGF23 level strongly suggests tumor recurrence.

There are only two reports that calculated the half-life (21.5-58 minutes) [21, 22]. Takeuchi et al.
Fig. 4  Serial measurements of serum FGF23 level and calculation of its half-life

(a) Serum FGF23 level, which was elevated preoperatively, swiftly dropped as early as 20 minutes after resection of the tumor and became undetectable for a few days postoperatively. Then it came back almost normal after 2 weeks. Medial cubital vein was used to take the blood samples. (b) The exponential curve of FGF23 levels indicates that the behavior of FGF23 fits single phase exponential decay model well. The half-life of FGF23 is calculated to be 18.4 minutes. (c) FGF23 levels before as well as 20 and 60 minutes after resection are plotted to a logarithmic graph. Using the semilog transformation formula as shown, the half-life of FGF23 is calculated to be 18.9 minutes.
Table 1 Literature review

<table>
<thead>
<tr>
<th>Case</th>
<th>Authors &amp; year</th>
<th>Age</th>
<th>Sex</th>
<th>Tumor location</th>
<th>Size (mm)</th>
<th>Diagnosis</th>
<th>Immunohistochemistry</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>David et al., 1996</td>
<td>60</td>
<td>F</td>
<td>Frontal base</td>
<td>N/A</td>
<td>PMTMCT</td>
<td>vimentin+ cytokeratin-EMA- S100- chromogranin A- desmin- factorVIII Ham56</td>
<td>Hip pain</td>
</tr>
<tr>
<td>2</td>
<td>Gonzalez-Compta et al., 1998</td>
<td>69</td>
<td>F</td>
<td>Ethmoid sinus, anterior fossa</td>
<td>N/A</td>
<td>PMTMCT</td>
<td>N/A</td>
<td>Bone pain, walking difficulty</td>
</tr>
<tr>
<td>3</td>
<td>Sandhu et al., 2000</td>
<td>46</td>
<td>M</td>
<td>Cribriform plate, ethmoid sinus</td>
<td>N/A</td>
<td>Hemangiopericytoma</td>
<td>SMA+ vimentin+ NSE+ keratin-CD34- EMA- GFAP- S100- Leu7- chromogranin-desmin-</td>
<td>Multiple fractures</td>
</tr>
<tr>
<td>4</td>
<td>Reis-Filho et al., 2004</td>
<td>47</td>
<td>F</td>
<td>Cavernous sinus</td>
<td>30</td>
<td>PMTMCT</td>
<td>CD34- EMA- MSA+ desmin- S100- CD68-</td>
<td>Muscle pain and weakness, visual disturbance</td>
</tr>
<tr>
<td>5</td>
<td>Yoshioka et al., 2006</td>
<td>45</td>
<td>M</td>
<td>Clivus</td>
<td>N/A</td>
<td>PMTMCT</td>
<td>N/A</td>
<td>Neck pain, XII palsy</td>
</tr>
<tr>
<td>6</td>
<td>Kaylie et al., 2006</td>
<td>46</td>
<td>F</td>
<td>Jugular foramen</td>
<td>N/A</td>
<td>PMTMCT</td>
<td>N/A</td>
<td>Tinnitus, vertigo, multiple fractures, bone pain</td>
</tr>
<tr>
<td>7</td>
<td>Uno et al., 2011</td>
<td>61</td>
<td>M</td>
<td>Cribriform plate</td>
<td>22</td>
<td>PMTMCT</td>
<td>FGF23+ CD34- EMA-PR-</td>
<td>Pain in entire body</td>
</tr>
<tr>
<td>8</td>
<td>Uno et al., 2011</td>
<td>53</td>
<td>F</td>
<td>Temporal bone</td>
<td>20</td>
<td>PMTMCT</td>
<td>FGF23+ CD34- EMA-PR-</td>
<td>Pain in entire body</td>
</tr>
<tr>
<td>9</td>
<td>Andreopoulou et al., 2011</td>
<td>63</td>
<td>F</td>
<td>Cribriform plate</td>
<td>N/A</td>
<td>No surgery</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10</td>
<td>Kobayashi et al., 2011</td>
<td>53</td>
<td>F</td>
<td>Temporal bone</td>
<td>N/A</td>
<td>PMTMCT</td>
<td>FGF23+</td>
<td>Bone pain, muscle weakness</td>
</tr>
<tr>
<td>11</td>
<td>Battoo et al., 2012</td>
<td>34</td>
<td>F</td>
<td>Cribriform plate, ethmoid sinus, nasal cavity</td>
<td>N/A</td>
<td>Giant cell tumor</td>
<td>vimentin+ S100- EMA- synaptophysin-chromogranin-leukocyte common antigen-</td>
<td>Muscle weakness, epistaxis, nasal blockage</td>
</tr>
<tr>
<td>12</td>
<td>Bower et al., 2012</td>
<td>67</td>
<td>F</td>
<td>Cribriform plate, frontal base</td>
<td>74</td>
<td>PMTMCT</td>
<td>FGF23+ vimentin+ S100- EMA- GFAP- CD34- SMA- CAM 5.2- desmin-CD31-MIB- 1low</td>
<td>Depression, urinary and fecal incontinence, apathy, abulia</td>
</tr>
<tr>
<td>13</td>
<td>Chokkyu et al., 2012</td>
<td>57</td>
<td>M</td>
<td>Sphenoid ridge</td>
<td>27</td>
<td>PMTMCT</td>
<td>N/A</td>
<td>Multiple fractures</td>
</tr>
<tr>
<td>14</td>
<td>Tarasova et al., 2013</td>
<td>67</td>
<td>F</td>
<td>Lt frontal base</td>
<td>17</td>
<td>No surgery</td>
<td>N/A</td>
<td>Pain in entire body, multiple fractures, muscle weakness</td>
</tr>
<tr>
<td>15</td>
<td>Mathis et al., 2013</td>
<td>28</td>
<td>F</td>
<td>Cribriform plate</td>
<td>18</td>
<td>PMTMCT</td>
<td>FGF23+ SMA+ CD34- EMA- S100-</td>
<td>Back stiffness, muscle weakness</td>
</tr>
<tr>
<td>16</td>
<td>Mathis et al., 2014</td>
<td>32</td>
<td>M</td>
<td>Cribriform plate, ethmoid sinus, nasal cavity</td>
<td>N/A</td>
<td>PMTMCT</td>
<td>FGF23+ SMA+ vimentin+ CD34- EMA- GFAP- synap- collagenIV- keratin-</td>
<td>Hip and low back pain</td>
</tr>
<tr>
<td>17</td>
<td>Gulwani et al., 2014</td>
<td>40</td>
<td>F</td>
<td>Clivus</td>
<td>N/A</td>
<td>Lipomatous hemangiopericytoma</td>
<td>vimentin+ CD34+ EMA- GFAP- factorVIII-</td>
<td>Headache, alerted sensorium</td>
</tr>
<tr>
<td>18</td>
<td>(Current case) Current study</td>
<td>38</td>
<td>F</td>
<td>Cribriform plate</td>
<td>10</td>
<td>PMTMCT</td>
<td>FGF23+ CD34- EMA- S100-</td>
<td>Pain in entire body, muscle weakness</td>
</tr>
</tbody>
</table>

Abbreviations: PMT, phosphaturic mesenchymal tumor, mixed connective tissue variant; N/A, not available.
calculated the half-life of FGF23 as 21.5 minutes using semilog transformation equation [22], which fits well with our result. Khosravi et al. used a single phase exponential decay model and calculated the half-life as 46-58 minutes [21]. They claimed that their methods fit better than semilog transformation equation used by Takeuchi et al. The large difference in the values between the above two studies may simply reflect the different methods used for calculation and/or individual variation in FGF23 clearance [21]. In this study, the above two mathematical models resulted in the very similar values, which were also consistent with the study by Takeuchi et al., and therefore we determined the half-life as approximately 18.5 minutes. Serum iron level and renal function are reported to effect the synthesis, degradation and clearance of serum FGF23 [23]. These factors may have led to the difference of calculation result between the current study and the previous reports [21, 22]; however, the lack of detailed data in the previous reports precludes further analysis. The short half-life of FGF23 may potentially allow intraoperative rapid assessment of the residual tumor once a reliable testing with a short turn-around time after tumor removal may indicate that intraoperative assessment of FGF23 level would help us predict the extent of resection and the possible cure of this endocrinologically active tumor.

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Disclosure

All authors have no conflict of interest.

References

The half-life of serum FGF23


