CASE REPORT

Unexplained Serum Iron Elevation After Neoadjuvant Chemotherapy in Pancreatic Cancer

Lili Zhan, Xinjia Cai, Yanan Zhang

Department of Clinical Laboratory Medicine, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China

SUMMARY

Background: Pancreatic ductal adenocarcinoma (PDAC) is a malignant tumor originating from the epithelium of the pancreatic duct. Neoadjuvant chemotherapy FOLFIRINOX (a combination of oxaliplatin, irinotecan, and 5-fluorouracil/leucovorin) is considered to be the most effective regimen for patients with resected pancreatic cancer.

Methods: This article reports a case of a pancreatic ductal adenocarcinoma patient who exhibited regular periodic fluctuations in the serum iron level during FOLFIRINOX.

Results: It indicates that an unexplained increase in serum iron levels after each cycle of FOLFIRINOX is non-cell destructive and due to a reduction in iron consumption, after ruling out other potential causes.

Conclusions: FOLFIRINOX in pancreatic cancer patients may cause an elevation of serum iron levels.

(KEYWORDS) pancreatic cancer, chemotherapy, FOLFIRINOX, serum iron

CASE REPORT

On February 1, 2023, a 66-year-old male patient underwent a contrast-enhanced CT scan for abdominal pain, which revealed a mass (24 mm x 14 mm x 17 mm) in the body of his pancreas. Considering the patient’s CA19-9 serum level was 122 U/mL (reference range < 27.0 U/mL) and further PET-CT imaging showed a slightly hyperdense nodular lesion in the pancreas. The surgeon performed laparoscopic distal pancreatectomy and splenectomy on February 15, 2023. Then this patient was diagnosed with moderately differentiated pancreatic ductal adenocarcinoma and was staged at T2N0, according to his postoperative pathology. The immunohistochemical analysis revealed positive staining for CK19 (3+), CK7 (3+), HER2 (2+), 20% Ki-67 (+), MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), and negative staining for CK20 (-) and PD-L1 (-). On April 2023, the patient was implanted with a chemo port and
received FOLFIRINOX (110 mg oxaliplatin, 260 mg irinotecan, 700 mg calcium folinate, and 4.0 g 5-fluorouracil) after excluding contraindications to chemotherapy. In order to monitor the patient's response to chemotherapy, blood tests, including complete blood count (CBC) and liver function tests (LFTs), are typically performed before and after each cycle of chemotherapy. Partial test results are presented in the Table 1 below. By retrospectively reviewing the biochemical test results, we discovered an unexplained elevation of serum iron levels in the patient after undergoing FOLFIRINOX (Figure 1). This elevation did not appear to be related to cellular destruction, as the patient's LFTs and CBCs were either normal or unchanged.

DISCUSSION

Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer and is known for its aggressiveness and poor prognosis [1]. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and shows good performance status [2,3]. In this case, we present a patient with pancreatic malignancy who underwent blood tests before and after FOLFIRINOX, and was found to have regular periodic fluctuations in serum iron levels. Given the high frequency of elevated serum iron levels in this patient, we thoroughly investigated the factors that could contribute to this result, such as personnel, reagents, equipment, procedures, quality control, and environment. However, we determined that the likelihood of any of these factors causing the issue was minimal. Our laboratory staff has extensive experience in biochemical testing, and we maintain our equipment in good operating condition with regular calibration and quality control procedures. The serum iron reaction curve was normal, and no alarm messages were detected. Furthermore, the sample did not exhibit any abnormal characteristics, such as hemolysis. To check for interference in the reagents, we reviewed the instructions for the Roche test reagents used with the Roche Cobas c702 (Germany) biochemical analyzer. We found no evidence of interference at therapeutic concentrations, as verified by common drug panels [4,5]. It was important to note that we were confident in the accuracy and reliability of the serum iron results.

Iron is one of the essential trace elements in the human body, playing an important role in cellular respiration, DNA synthesis, enzyme activity, and the synthesis of hemoglobin [6,7]. As an indicator of iron metabolism, serum iron reflects the iron bound to transferrin in the blood and is one of the methods used to evaluate anemia and other iron metabolism-related diseases [8]. The content of serum iron is regulated by various factors. Since there were no abnormalities detected in the testing procedure and specimen condition, we analyzed the reason for the increase in serum iron levels from the perspective of iron metabolism, including iron intake, storage, and utilization. After communicating with the patient's attending physician, we obtained some detailed information. Common clinical reasons for elevated serum iron levels include excessive iron intake, vitamin B6 or B12 intake, Mediterranean anemia, hemolytic anemia, hepatitis, iron-deficiency anemia, lead poisoning, and others. However, this patient did not use any iron-containing medications, so iron intake is not considered a cause of the increase. Additionally, there was no hepatosplenomegaly, and the blood routine did not indicate microcytic hypochromic anemia and showed normal white blood cells and platelets. Since there is no history of lead exposure, iron utilization disorders are not considered.

Hemoglobin levels were stable, and biochemical liver function parameters such as AST and ALT suggest no liver cell damage, so excessive iron release caused by red blood cells or liver cells is not considered. Upon reviewing the previous medical records, the doctor supported the conclusion that chemotherapy drugs were responsible for the elevation of serum iron levels. Nevertheless, the exact mechanisms by which chemotherapy drugs increase serum iron levels are not yet fully understood.

Further literature review revealed that T. Ochiai et al. had previously investigated serum iron, ferritin, AST, ALT, hemoglobin, hepcidin-25, IL-6, and soluble transferrin receptor (sTfR) levels in advanced colorectal cancer patients treated with FOLFOX (fluorouracil + oxaliplatin + calcium folinate)/FOLFIRI (irinotecan + fluorouracil + calcium folinate) before and 48 hours after chemotherapy. They found that serum iron and hepcidin-25 levels significantly increased (p < 0.0001) after chemotherapy, while IL-6 levels significantly decreased (p = 0.0057), with no significant changes in the other parameters [9,10]. Moreover, the increase in serum iron was a reproducible event. Further studies conducted by them indicated that the observed increase in serum iron during chemotherapy was caused by the chemotherapy drugs inhibiting the production of mature red blood cells. As a result, there was a reduction in iron consumption, which led to an increase in serum iron levels and subsequently caused an elevation in hepcidin-25 levels. Additionally, the levels of sTfR showed no significant difference before and after chemotherapy, indicating that the production of immature red blood cells was not significantly affected by the treatment [10]. For hepcidin-25 level, when the production of red blood cells is normal, hemolysis and anemia lead only to a reduction. However, if red blood cell production is completely suppressed, hepcidin levels will increase significantly. Red blood cell suppression can occur in diseases such as acute leukemia, aplastic anemia, pure red cell aplasia, and myelodysplastic syndrome. In such cases, serum iron levels may remain high despite the presence of anemia. T. Ochiai's study also revealed that patients receiving FOLFOX/FOLFIRI who showed a greater increase in serum iron had a significantly longer median survival time compared to those who did not. Multivariate analysis indicated that even a slight increase in se-
Serum Iron Rise Post-Chemo in Pancreatic Cancer

Table I. Changes in the patient's laboratory test values.

<table>
<thead>
<tr>
<th>Date</th>
<th>Fe (µmol/L)</th>
<th>ALT (U/L)</th>
<th>AST (U/L)</th>
<th>RBC (x10⁹/L)</th>
<th>HB (g/L)</th>
<th>HCT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(5.83 - 34.5)</td>
<td>(0 - 41)</td>
<td>(0 - 40)</td>
<td>(4.3 - 5.8)</td>
<td>(130 - 175)</td>
<td>(40 - 50)</td>
</tr>
<tr>
<td>2023-04-07</td>
<td>8.97</td>
<td>12.2</td>
<td>16.9</td>
<td>4.09</td>
<td>119 ↓</td>
<td>35.7 ↓</td>
</tr>
<tr>
<td>2023-04-17</td>
<td>45.68 ↑</td>
<td>26.4</td>
<td>48.1 ↑</td>
<td>3.75</td>
<td>109 ↓</td>
<td>32.7 ↓</td>
</tr>
<tr>
<td>2023-04-28</td>
<td>10.65</td>
<td>17.6</td>
<td>16.9</td>
<td>3.55</td>
<td>102 ↓</td>
<td>30.5 ↓</td>
</tr>
<tr>
<td>2023-05-01</td>
<td>45.02 ↑</td>
<td>13.8</td>
<td>15.7</td>
<td>3.64</td>
<td>106 ↓</td>
<td>31.2 ↓</td>
</tr>
<tr>
<td>2023-05-14</td>
<td>6.81</td>
<td>16.4</td>
<td>24.2</td>
<td>3.84</td>
<td>112 ↓</td>
<td>34.0 ↓</td>
</tr>
<tr>
<td>2023-05-17</td>
<td>32.64</td>
<td>18.7</td>
<td>31.0</td>
<td>3.76</td>
<td>111 ↓</td>
<td>33.0 ↓</td>
</tr>
<tr>
<td>2023-06-09</td>
<td>11.82</td>
<td>24.6</td>
<td>27.3</td>
<td>3.66</td>
<td>110 ↓</td>
<td>32.4 ↓</td>
</tr>
<tr>
<td>2023-06-12</td>
<td>54.49 ↑</td>
<td>21.8</td>
<td>32.1</td>
<td>3.77</td>
<td>114 ↓</td>
<td>33.1 ↓</td>
</tr>
</tbody>
</table>

Fe - serum iron, ALT - alanine aminotransferase, AST - aspartate aminotransferase, RBC - red blood cell, HB - hemoglobin, HCT - hematocrit.

Figure 1. The level of serum iron.

Serum iron was an independent risk factor for overall survival, whereas molecular targeted drugs did not have such an effect on serum iron levels. Therefore, serum iron levels may serve as a powerful predictive factor for the response to FOLFOX/FOLFIRI chemotherapy. Based on the literature review above, it is plausible that the observed increase in serum iron levels in this patient is a result of FOLFIRINOX treatment, which may have suppressed the production of red blood cells and subsequently reduced iron consumption. However, the precise mechanism by which FOLFIRINOX inhibits iron consumption in red blood cell production over a short period of time remains to be elucidated.
CONCLUSION

Various factors can influence serum iron levels, such as diet, medication, disease, and genetic factors. Therefore, in clinical practice, increased serum iron levels are often associated with excessive iron intake, hemolytic anemia, hepatitis, lead poisoning, and other conditions. For cancer patients, it is noted that fluctuations in serum iron levels are related to FOLFIRINOX/FOLFOX/FOLFIRI chemotherapy. This study is important for understanding the effects of FOLFIRINOX chemotherapy on iron metabolism in cancer patients and may have implications for the management of iron disorders in this population.

Source of Support:
This work was supported by Shenzhen High-level Hospital Construction Fund.

Declaration of Interest:
No conflicts of interest.

References: