Serum Tumor Marker CA 125 Is an Early and Sensitive Indicator of Veno-Occlusive Disease in Children Undergoing Bone Marrow Transplantation

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ABSTRACT

Veno-occlusive disease (VOD) is a potentially lethal complication of patients undergoing bone marrow transplantation (BMT). The diagnosis of VOD is currently based on clinical signs and unspecific laboratory findings. CA 125 is an oncofetal antigen used as a tumor marker in various malignancies, especially in those originating from the female reproductive tract or gastrointestinal organs, whereas serum CA 125 levels are not increased in hematological malignancies. Several pathophysiological alterations occurring in VOD may lead to elevations in serum CA 125 levels. Therefore, we explored the behavior of this marker as a diagnostic tool in VOD. Twenty-nine pediatric transplant patients were studied. Eight patients (28%) developed clinical VOD, and a significant increase in serum CA 125 was noted in all of them. During the 7 days preceding the diagnosis of VOD, an increase of at least 57% in serum CA 125 from the pre-BMT value was observed in 6 (86%) of 7 of the evaluable patients with VOD. In contrast, a similar increase was noted in only 6 of the 21 non-VOD patients during the post-BMT period of 30 days. Accordingly, the sensitivity and specificity of serum CA 125 for predicting or detecting VOD were 86% and 71%, respectively. The serum levels of CA 125 were not affected by the presence of Graft-versus-Host Disease (GvHD) or a septic infection. In conclusion, serum CA 125 is of value as an early marker of VOD in children undergoing BMT.

INTRODUCTION

VOD is a potentially life-threatening complication of BMT in children and adults with a mortality of 10–50% (1–3). It typically presents with abdominal pain, ascites, weight gain, and liver dysfunction. Whereas increase in serum bilirubin is characteristic of VOD, such an elevation is also often noted in GvHD; overall, the traditional clinical parameters lack the sensitivity and specificity required for the timely diagnosis of VOD (reviewed in Ref. 1), and additional early indicators would thus, be desirable for differential diagnosis of VOD. Recently, encouraging results by monitoring serum levels of procollagen type III (4, 5), protein C (6), or plasminogen activator inhibitor-1 (7) have been published. In the present study, we have focused on serum oncofetal antigen CA 125 in search for new markers for VOD in children undergoing BMT.

The monoclonal antibody recognizing CA 125 antigen was originally raised against an ovarian cystadenocarcinoma cell line (8, 9). The exact antigenic structure defined by these antibodies has remained unknown thus far. CA 125 has characteristics of an oncofetal antigen as revealed by its expression in certain fetal tissues (10–12) and in association with various malignancies, especially those originating from the female reproductive tract or gastrointestinal organs (reviewed in Refs. 13–15). Pediatric patients with germ cell tumor or abdominal Burkitt’s lymphoma can also present with elevated serum CA 125 levels at diagnosis (16, 17).

Clinically, serum CA 125 measurements have been used mainly in the diagnosis and follow-up of ovarian and gastrointestinal cancers (reviewed in Ref. 13). Benign conditions such as endometriosis (18) and pelvic inflammations (19) can, however, also increase serum CA 125 levels. Other nonmalignant conditions associated with elevated serum CA 125 levels include acute pancreatitis, peritonitis, renal failure, and various gynecological and liver diseases (15, 20–23). Low levels of CA 125 can also be detected in the serum of healthy individuals (17).

Besides malignancies, CA 125 is synthesized in some normal tissues, including fetal intrahepatic bile ducts and adult endometrium, pleura, and peritoneum (reviewed in Ref. 24). Given the two potential anatomical sources for CA 125 synthesis—namely intrahepatic bile ducts and peritoneum, both affected by the pathogenetic mechanisms during VOD—we hypothesized that CA 125 might be increased in this disease. The second prerequisite for the potential value of this marker as an indicator of VOD is that the clinical conditions that are indications for pediatric BMT would not per se be associated with

Received 7/19/99; revised 11/10/99; accepted 11/15/99.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 Supported by grants from the Finnish Pediatric Foundation [to S. P. and M. H.], and from the Helsinki University Central Hospital Fund to [J. P., K. V., M. H.]; 2 Present address: Department of Dermatology, University of Helsinki, 00290 Helsinki, Finland; 3 To whom requests for reprints should be addressed, at Children’s Hospital, University of Helsinki, Stenbäckinkatu 11, 00290 Helsinki, Finland. Phone: 358-9-4717-4768; Fax: 358-9-4717-5299; E-mail: markku.heikinheimo@helsinki.fi
increased levels of CA 125. Because there was no indication that this would be the case, we tested whether CA 125 might be of value in the diagnosis of VOD. In the present study, we demonstrate that VOD is associated with significantly increased serum CA 125. Whereas the mechanisms of the increase in CA 125 are probably multiple, the rise in serum CA 125 during the early course of VOD makes it a feasible marker of this diagnostically challenging condition.

PATIENTS AND METHODS

Patients

Twenty-nine patients who underwent 32 BMT procedures, either at the Children’s Hospital, University of Helsinki, Finland (19 patients) or at the Department of Pediatrics, University of Göteborg, Sweden (10 patients), were included in this study. In both institutions, the patients were recruited in a consecutive manner. However, in Helsinki, 7 patients were studied in 1997–1998 and 12 patients in 1986–1990. Selected clinical data of the patients are given in Table 1. Three of the children had two transplants (no. of transplants)

### Table 1 Clinical data on the patients included in the study (studied for serum CA 125)†

| No. of marrow transplants (no. of patients) | 32 (29) |
| Female/male ratio | 14/15 |
| Mean age, yr (range) | 6.2 (0.1–17.2) |
| Diagnosis (no. of patients) | |
| Acute lymphoblastic leukemia | 9 |
| Acute myelogenous leukemia | 3 |
| Lymphoma | 2 |
| Neuroblastoma | 4 |
| Retinoblastoma | 1 |
| Small round cell tumor | 2 |
| Other solid tumor | 3 |
| Osteopetrosis | 3 |
| Kostman’s syndrome | 1 |
| Combined immunodeficiency | 1 |
| BMTs (no. of transplants)§ | |
| Allogeneic (HLA matched/HLA mismatched) | 3/15 |
| Autologous | 14 |

† Twenty-two of the patients were the same as in a study previously reporting serum procollagen type III as a marker of VOD (6).

§ Allogeneic donors were considered matched if identical at HLA loci A, B, C, and DRB1.

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21 non-VOD patients was noted in only 6 patients before the evaluable VOD patients. In contrast, such an increase in the 125 from the pre-BMT value was observed in 6 (86%) of 7 of diagnosis included), an increase of 57% or more in serum CA 7-day period preceding the diagnosis of VOD (the day of first post-VOD CA 125 level was significantly increased (by 2.1-fold) when compared with the pre-BMT value. Because of the lack of a representative sample, this patient was excluded from the sensitivity and specificity calculations. During the 7-day period preceding the diagnosis of VOD (the day of diagnosis included), an increase of 57% or more in serum CA 125 from the pre-BMT value was observed in 6 (86%) of 7 of the evaluable VOD patients. In contrast, such an increase in the 21 non-VOD patients was noted in only 6 patients before the day-30 post-BMT (the limit for VOD by definition). Thus, with this cutoff level, the sensitivity and specificity of serum CA 125 for predicting or detecting VOD were 86 and 71%, respectively. When an absolute increase of at least 17 units/ml from the pre-BMT value in CA 125 was used as a cutoff, the sensitivity remained at 86%, but the specificity increased to 76%.

**Serum CA 125 in Children with GvHD or Severe Infections.** Four patients developed a grade II-to-IV GvHD, on average, 24 days after BMT (range, 12–48 days). Elevated levels of serum CA 125 were observed in several samples from these patients (Fig. 2B). However, serum CA 125 level did not detect or predict GvHD. During the week preceding the diagnosis of GvHD, serum CA 125 was increased by 0–42% when compared with the pre-BMT value. One of the GvHD patients, who developed acute GvHD on day 48 post-BMT, was diagnosed as having VOD on day 14. The organ-specific sequence of GvHD did not affect the serum CA 125 pattern; the serum CA 125 values obtained during the consecutive 1-week periods (the indicated day ± 3 days) were pooled for the analysis. For each patient, the serum CA 125 value that was obtained closest to the indicated time point was used.

VOD, and, in 6 of 8 VOD patients, the increase either preceded or coincided with the diagnosis of VOD (Fig. 2A). One patient was diagnosed with VOD on post-BMT day 6, and no CA 125 sample was drawn between BMT and VOD. In this patient, the first post-VOD CA 125 level was significantly increased (by 2.1-fold) when compared with the pre-BMT value. Because of the lack of a representative sample, this patient was excluded from the sensitivity and specificity calculations. During the 7-day period preceding the diagnosis of VOD (the day of diagnosis included), an increase of 57% or more in serum CA 125 from the pre-BMT value was observed in 6 (86%) of 7 of the evaluable VOD patients. In contrast, such an increase in the 21 non-VOD patients was noted in only 6 patients before the

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**Table 2 Clinical and laboratory data of VOD patients**

<table>
<thead>
<tr>
<th>F/M Diagnosis</th>
<th>Age (yr)</th>
<th>BM Ttype</th>
<th>GvHD (day)</th>
<th>VOD (day)</th>
<th>Infection</th>
<th>Ascites</th>
<th>Edema</th>
<th>Weight gain</th>
<th>Hep. meg.</th>
<th>Outcome</th>
<th>Maximum bilirubin</th>
<th>CA 125, units/ml</th>
<th>pre-BMT/maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>F Kostman</td>
<td>2.6</td>
<td>Allo</td>
<td>23</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Died</td>
<td>175</td>
<td>30/320</td>
<td>Died</td>
<td>111</td>
<td>111</td>
<td>11</td>
</tr>
<tr>
<td>F Osteopetrosis</td>
<td>0.3</td>
<td>Allo</td>
<td>19</td>
<td>+(CMV)</td>
<td>+</td>
<td>+</td>
<td>Died</td>
<td>32</td>
<td>15/35</td>
<td>Died</td>
<td>111</td>
<td>111</td>
<td>11</td>
</tr>
<tr>
<td>M Osteopetrosis</td>
<td>0.1</td>
<td>Allo</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Recov</td>
<td>77</td>
<td>15/150</td>
<td>Recov</td>
<td>77</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>M SCID</td>
<td>0.5</td>
<td>Allo</td>
<td>13</td>
<td>+(BCG)</td>
<td>+</td>
<td>+</td>
<td>Died</td>
<td>490</td>
<td>23/200</td>
<td>Died</td>
<td>490</td>
<td>490</td>
<td>490</td>
</tr>
<tr>
<td>F AML</td>
<td>4.6</td>
<td>Auto</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Recov</td>
<td>30</td>
<td>15/21</td>
<td>Died</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>M ALL</td>
<td>1.1</td>
<td>Allo</td>
<td>30</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Died</td>
<td>18</td>
<td>15/220</td>
<td>Died</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>M Gioma</td>
<td>12.2</td>
<td>Auto</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Died</td>
<td>95</td>
<td>20/63</td>
<td>Died</td>
<td>95</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>F</td>
<td>1.4</td>
<td>Allo</td>
<td>48</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>Recov</td>
<td>52</td>
<td>15/47</td>
<td>Died</td>
<td>52</td>
<td>52</td>
<td>52</td>
</tr>
</tbody>
</table>

* Hep.meg., hepatosplenomegaly; Allo, allogenic; Auto, autologous; CMV, cytomegalovirus; BCG, Bacillus Calmette-Guérin; SCID, severe combined immunodeficiency; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; Recov, recovered.
Considering the potential mechanisms of CA-125 increases, we were especially interested in its associations with liver and renal functions. There were no significant correlations between serum CA 125 and alanine aminotransferase, aspartyl aminotransferase, or thromboplastin time. Somewhat surprisingly, a moderate negative correlation was observed between alkaline phosphatase and CA 125 ($r = -0.251; P < 0.05; n = 71$). Serum creatinine correlated positively ($r = 0.292; P < 0.05; n = 73$), and serum albumin correlated negatively with CA 125 ($r = -0.349; P < 0.001; n = 117$). There was a moderate positive correlation between serum procollagen type III and CA 125 ($r = 0.185; P < 0.05; n = 139$).

**DISCUSSION**

In the present study, we have evaluated the value of serum CA 125 determinations in the diagnosis of VOD in children undergoing BMT. Thus far, the studies on the role of CA 125 in children have focused on its use as a diagnostic tool in cancer. These studies have demonstrated that serum CA 125 may be elevated in children with premalignant or malignant liver diseases (27, 28) and in some patients with immature teratomas or germ-cell tumors (17). The sites of origin of CA 125 antigen in these patient groups are not clear, but the fetal type of gene expression in tumors is a possible explanation for elevated serum CA 125 in children with embryonal tumors. Abdominal Burkitt’s lymphoma in children and adults is also often associated with increased serum CA 125 concentration at diagnosis (16, 29).

Our results demonstrate that serum CA 125 measurement can be used as an early and sensitive indicator of VOD. Importantly, the main clinically relevant processes to be considered as differential diagnostic options for VOD did not cause significant rapid changes in serum CA 125 levels. However, as is evident from Fig. 2, A and B, the clinical usefulness of CA 125 measurement may depend on repeated measurements because VOD was associated with rapid increase from the baseline level whereas the maximum concentrations achieved were not invariably high. Therefore, we want to underscore that a follow-up of CA 125 levels is mandatory and is far more informative than single estimations. Although there is currently no effective therapy available for established VOD in the BMT setting, its timely and reliable differentiation from other, and possibly concurrently, emerging processes, such as acute GvHD, remains paramount clinical importance.

The mechanisms of CA 125 increase in the VOD patients remains unspecified thus far but most likely are multiple. Unspecific rise due to hepatocellular damage is unlikely because no correlation between CA 125 and aminotransferases or thromboplastin time were found. Our original hypothesis included altered CA 125 synthesis in intrahepatic bile ducts. However, the negative correlation between CA 125 and alkaline phosphatase does not support this assumption. Ascites formation is a central criterion for VOD. Given that the peritoneum synthesizes CA 125 antigen (30), we hypothesized that, irrespective of whether ascites formation in VOD involves irritation of peritoneal epithelium or merely reflects passive stasis at the hepatic level, altered homeostasis of peritoneal epithelium might affect CA 125 synthesis. Supporting this hypothesis, we observed a significant negative correlation between the serum albumin and CA 125 levels. Finally, decreased renal clearance may contribute to the increased levels of serum CA 125 because a positive correlation was found between serum CA 125 and creatinine levels.
We and others have earlier shown that serum PIINP levels are elevated in most patients with VOD when or before the diagnostic criteria are fulfilled (4, 5), and that PIINP may, thus, serve as a marker for VOD. In the present study, we found a significant correlation between serum CA 125 and serum PIINP levels, and these two markers—probably reflecting the peritoneal and liver involvement, respectively—could, thus, be used to complement each other as biochemical indicators for VOD. Serum CA 125 was at least as sensitive a marker of VOD as serum PIINP, and the availability of the CA 125 determinations in most centers gives it an additional advantage over PIINP measurements. Yet, the final role of each of the putative new parameters, including PIINP, protein C, plasminogen activator inhibitor-1, and CA 125 in the clinical diagnosis of VOD remains to be established.

Taken together, our results demonstrate that the pathophysiological process in VOD leads to increased serum concentrations of CA 125 early in the disease in the vast majority of patients. These results suggest that the measurement of serum CA 125 is of benefit in diagnosing VOD in children undergoing BMT. With emerging new therapies for VOD, the identification of sensitive and easily measurable markers will probably be of great benefit in the management of these patients.

REFERENCES

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