Serum Creatine Kinase Levels Parallel the Clinical Course for Rhabdomyomatous Wilms Tumor

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Key Words: Wilms tumor; Nephroblastoma; Rhabdomyoblast; Creatine kinase; CK-MB; Tumor marker

Abstract

A right-sided renal mass in an 11-month-old girl was diagnosed by percutaneous needle biopsy as Wilms tumor, which on histologic examination was found to be predominantly rhabdomyomatous. As part of the examination, serum creatine kinase (CK) and CK-MB levels were measured and were significantly elevated at 994 U/L (reference range, 42-180 U/L) and 40 U/L (reference range, 0-3 U/L), respectively. Subsequently, an 8-month-old girl was admitted to the hospital with septicemia and was found to have an abdominal mass. A diagnosis of bilateral Wilms tumor was made following percutaneous biopsy of both kidneys; histologic examination confirmed that the tumor was predominantly rhabdomyomatous. Serum CK and CK-MB levels also were measured and were significantly elevated at 685 U/L and 84.4 U/L, respectively. In both cases, the serum CK and CK-MB levels reflected the clinical course; elevation in serum levels was associated with tumor recurrence, infarction, or chemotherapy-related necrosis. We conclude that these enzymes have clinical usefulness as markers for Wilms tumor showing rhabdomyomatous morphologic features.

Materials and Methods

The development of treatment protocols for Wilms tumor, resulting from the outcomes of the 4 National Wilms Tumor Studies, is arguably one of the great achievements in collaborative medicine of the 20th century, with 2-year relapse-free survivals now exceeding 91%.1 Treatment protocols based on the recommendations of the National Wilms Tumor Study depend on accurate staging of disease at the time of diagnosis, and, in addition, early detection of recurrent disease is essential to maximize favorable outcome. At present, staging relies on clinical, imaging, and surgical findings, and no marker for Wilms tumor that accurately predicts active disease has been described. A tumor marker ideally should be tumor specific and detectable at low levels, while levels should correlate with tumor mass and reflect clinical response to anticancer therapy.2 Although various tumor-related proteins have been detected in cases of Wilms tumor,3-11 none satisfy these criteria.

We studied the clinical usefulness of creatine kinase (CK) and the isoenzyme CK-MB as tumor markers for Wilms tumor showing rhabdomyomatous differentiation.

Case 1

An 11-month-old girl was first seen with a large right-sided abdominal mass. Abdominal computed tomography (CT) showed a large solid tumor arising from the anterior...
aspect of the right kidney involving two thirds of the abdomen and extending from the intrahepatic region to the right iliac fossa. The results of a chest radiograph, thoracic CT, and bone marrow biopsy were normal. As part of the biochemical studies, serum total CK and isoenzyme CK-MB levels were measured and were markedly elevated. Trucut biopsy (Allegiance Healthcare, McGaw Park, IL) of the renal mass was undertaken with vincristine prophylaxis to prevent tumor spread, and a diagnosis of rhabdomyomatous Wilms tumor was made.

**Case 2**

An 8-month-old girl was taken to her family practitioner with varicella, and clinical examination revealed bilateral abdominal masses. There was no clinical evidence of Wilms tumor predisposition syndrome. Results of a chest radiograph, thoracic CT, and bone marrow biopsy were normal. Abdominal ultrasonography and CT showed bilateral renal tumors, and a diagnosis of bilateral Wilms tumor was confirmed following percutaneous biopsy.

**CK Assays**

Quantitative analysis of total CK for each patient was undertaken by the standardized reverse reaction and activation by acetyl-cysteine performed on a Hitachi 717 autoanalyzer (Boehringer Mannheim GmbH, Mannheim, Germany) using Roche Diagnostic CK NAC analyzer kits (Roche Diagnostic, Indianapolis, IN). For case 1, ion-exchange column chromatography was used for identification and quantitation of CK-MB.12 Quantitative analysis of CK-MB in case 2 was performed by standard 2-site sandwich immunoassay and direct chemiluminescence (ACS: 180, Chiron Diagnostics, Norwood, MA).

**Results**

**Case 1**

At the time of admission and before renal biopsy and commencement of treatment, the total CK level was 994 U/L (reference range, 42-180 U/L), while the CK-MB level was 40 U/L (reference range, 0-3 U/L). Preoperative chemotherapy (actinomycin D, vincristine, and doxorubicin) was given, but there was no reduction in tumor size. During this period, serum CK levels fell to 255 U/L, while the serum CK-MB level fell to 8 U/L. Almost 2 months after initial examination, elective right nephrectomy was undertaken. In the immediate postoperative period, the serum CK level was markedly elevated at 1,410 U/L, and this level fell rapidly to normal, while the serum CK-MB level remained at 8 U/L. Postoperatively, 6 cycles of ifosfamide and etoposide chemotherapy with mesna protection was completed without complication. At the commencement of this postoperative chemotherapy, total serum CK and serum CK-MB levels rose to 404 U/L and 14 U/L, respectively. The total serum CK level then declined to normal levels during 6 weeks, while the serum CK-MB level reached 4 U/L after 18 weeks. The patient has been followed up for 10 years and is tumor free. During this period, serum CK and serum CK-MB levels have remained normal. Total serum CK and serum CK-MB levels in relation to the patient’s clinical course are summarized in [Figure 1](#).

**Case 2**

At the time of admission, the serum CK level was 390 U/L and increased to 685 U/L during the next 8 days. The CK-MB level 8 days after admission was 86 U/L ([Figure 2](#)). Preoperative chemotherapy (vincristine, actinomycin D, and doxorubicin) was undertaken and resulted in no reduction in tumor size as documented by ultrasonography. Levels of both serum CK and serum CK-MB fluctuated over this period, and by 11 weeks, the serum CK level was 293 U/L, and the serum CK-MB level was 16.3 U/L. Assessment of residual renal tissue by dimercaptosuccinic acid scan showed that the left kidney provided 84% of renal function. Partial left nephrectomy was planned, and selective angiography was undertaken. This procedure was complicated by the development of ileus with vomiting, and both ultrasound and diethylene triamine pentaacetic acid scan confirmed extensive tumor infarction with residual perfusion of the upper pole of the left kidney. At this time, the serum CK level was 12,453 U/L, and the serum CK-MB level was 242.9 U/L. Left partial nephrectomy was undertaken 72 hours later, and within 1 week of surgery, the serum CK and CK-MB levels fell to 81 U/L and 6.2 U/L, respectively. Postoperative recovery was complicated by the development of hypertension. Vincristine and actinomycin D chemotherapy was recommenced after the immediate postoperative period.

Significant growth in the right renal tumor was noted, and while the total serum CK level remained within the reference range, the serum CK-MB level increased to 17.3 U/L. Elective right nephrectomy was undertaken, and at operation, the tumor was found to be adherent to the liver and the diaphragm and was dissected free with difficulty. In the postoperative period, both total serum CK and serum CK-MB levels fell to normal levels and remained so for the remainder of the patient’s life.

Postoperative chemotherapy of vincristine and actinomycin D was given for 8 weeks, and the patient remained well while receiving antihypertensive therapy and erythropoietin. Seven months later, recurrent tumor developed in the residual left hemikidney, resulting in obstructive uropathy, and a nephrostomy tube was inserted. Needle biopsy
confirmed recurrent Wilms tumor, and 10 weeks’ treatment with vincristine, actinomycin D, and doxorubicin was followed by left heminephrectomy. The patient recovered well, and peritoneal dialysis was commenced. She remained clinically tumor free but was admitted 25 months later with clinical features of septicemia and died 12 hours later. Postmortem examination showed no evidence of tumor recurrence or extrarenal tumor.

Pathologic Findings

The diagnostic needle biopsy specimen from case 1 showed sheets of primitive mesenchyme intermingled with rhabdomyoblasts and occasional nests of poorly formed tubules Image 1. Scattered areas of necrosis but no anaplasia were seen, and a diagnosis of rhabdomyomatous Wilms tumor was made. The right nephrectomy specimen contained a tumor mass $16 \times 12 \times 10$ cm expanding the lower renal pole. Microscopy showed that the tumor consisted of nests of skeletal muscle within a fibrous stroma. Occasional islands of blastema and primitive neoplastic tubules also were present. No anaplasia was seen, and the tumor was confined to the kidney with no evidence of nodal involvement.

Biopsy specimens from the right and left renal tumors of case 2 showed immature mesenchyme with nests and sheets of rhabdomyomatous elements Image 2. Occasional small

Image 1 (Case 1) Diagnostic biopsy specimen. Tumor is composed predominantly of rhabdomyoblasts and contains occasional poorly differentiated epithelial nests (H&E, ×170).

Image 2 (Case 2) Diagnostic biopsy specimen, right kidney. Rhabdomyomatous Wilms tumor (H&E, ×170).
aggregates of primitive tubules and blastema without anaplasia were identified. The features were those of bilateral rhabdomyomatous Wilms tumor.

The left heminephrectomy specimen contained a pseudoencapsulated tumor 15.5 × 13 × 10 cm. The tumor consisted predominantly of stromal elements showing rhabdomyomatous, adipose, and fibroblastic differentiation. The skeletal muscle appeared more mature than that seen in the initial biopsy specimen [Image 3], and cytoplasmic cross-striations occasionally were visualized. Occasional nests of blastema and primitive epithelial elements were present. In some areas the tumor showed confluent necrosis, while elsewhere foci of dystrophic calcification and ossification were identified. The excision margins were free of tumor.

The right kidney contained a lobulated tumor mass 18 × 14 × 10 cm. This was fully contained within the central portion of the kidney with tumor prolapse into the caliceal system. Histologically, the tumor showed features similar to those of the left kidney with scant blastema and primitive tubular and glomeruloid epithelial nests in a stroma exhibiting extensive rhabdomyomatous differentiation and containing sheets of fibroblasts and islands of mature adipose tissue. As in the previous specimen, scattered areas of dystrophic calcification and ossification were seen. An enlarged caval node removed as part of the nephrectomy procedure showed reactive changes only.

Within the central portion of the residual left kidney there was a semispherical tumor mass 4.5 cm in diameter. The tumor was largely necrotic; however, viable neoplastic tissue was present at the periphery. This consisted of loose collagenous connective tissue containing nests of blastema and only scant skeletal muscle elements [Image 4].

Discussion

A variety of serum markers have been studied for clinical significance in adult and childhood renal tumors with differing results. The majority of these putative tumor markers have been associated with the various subtypes of renal cell carcinoma, and only rarely have childhood renal tumors been shown to secrete tumor-related proteins.3,13 Specifically, it has been noted that hyaluronic acid and an unidentified protein-polysaccharide complex was present in the serum and in the urine and serum, respectively, in patients with Wilms tumor and that protein levels correlated with tumor occurrence.4,5

Several paraneoplastic syndromes have been described in association with Wilms tumor, and this has led to the identification of tumor-related products that have been proposed as serum markers for this type of malignant neoplasm.3 In particular, elevated levels of adrenocorticotropic hormone,6 neuron-specific enolase,7 hyaluronic acid,8 erythropoietin,9 and renin10 have been correlated with clinical progress of the disease, while rare cases of tumor-associated acquired von Willebrand disease have led to speculation that this is also due to tumor-related protein.11 CK secretion by Wilms tumor seems not to have been studied to date, and the present cases are the first in which serum total CK and isoenzyme CK-MB levels have been correlated with clinical outcome in children with Wilms tumor.
Activity of the dipeptide enzyme CK is seen in a wide range of normal tissue, while activity of the isoenzyme CK-MB is more restricted, being ubiquitous in cardiac muscle. In both of our cases, there was no history of cardiac disease, and chemotherapy-related cardiomyopathy and cardiac ischemia were excluded by periodic electrocardiography and clinical examination. CK-MB has been observed occasionally in ovarian, hepatic, and gastric wall homogenates, and while in renal tissue activity of isoenzymes CK-MM and CK-BB has been reported, activity of CK-MB was not seen. In malignant tumors, total CK activity has been demonstrated in a variety of epithelial and stromal neoplasms, while CK-MB activity rarely has been seen and has specifically been shown to be absent in renal cell carcinoma of unspecified type and in transitional cell carcinoma of the renal pelvis. In other forms of malignant neoplasm, elevated serum levels of CK-MB have been rarely recorded, with reports confined to ovarian (1 case) and soft tissue (1 case) rhabdomyosarcoma, carcinoma of the lung (2 cases), carcinoma of the colon (2 cases), prostatic carcinoma (1 case) and colonic neuroendocrine tumor (1 case). In addition, low levels of CK-MB activity have been identified in homogenates from single cases of squamous cell carcinoma and adenocarcinoma of the lung, papillary and undifferentiated carcinoma of the ovary, hepatic cholangiocarcinoma, gastric adenocarcinoma, and liposarcoma.

Our 2 cases of rhabdomyomatous Wilms tumor both showed elevated serum total CK and CK-MB levels at the initial examination. In case 1, steady decline in serum levels of total CK and the CK-MB isoenzyme corresponded with administration of preoperative chemotherapy. Elective nephrectomy was associated with a massive increase in the total CK level, while the CK-MB level remained stable. It was initially considered that the observed elevation in the total CK level was the result of tumor manipulation, although the failure of the CK-MB level to increase provided evidence that the elevated total CK level was due to abdominal muscle transection. This hypothesis was confirmed subsequently in patients undergoing laparotomy for nonneoplastic diseases in whom a similar pattern of serum total CK elevation with serum CK-MB stability was observed, with the total CK changes corresponding to the timing of the operative procedure (data not shown). Within 5 weeks of operation, serum total CK and serum CK-MB levels were elevated above reference ranges, suggesting the presence of residual tumor, and these levels gradually declined with the administration of 6 cycles of etoposide and ifosfamide. Levels of serum total CK and serum CK-MB have remained normal for 10 years, and the patient remains clinically stable with no evidence of tumor recurrence.

In case 2, serum total CK and serum CK-MB levels were elevated at the initial examination, and, based on our previous experience, a presumed diagnosis of rhabdomyomatous Wilms tumor was made and was confirmed with renal biopsy. While no reduction in tumor size was noted during preoperative chemotherapy, fluctuation of the serum total CK level and a gradual decline in the serum CK-MB level was considered to represent chemosensitivity of myomatous elements or maturation of tumor tissue, the latter being a feature frequently seen in postchemotherapy Wilms tumor. Tumor infarction within the left kidney, which corresponded to massive increases in both serum total CK and serum CK-MB levels, necessitated urgent left partial nephrectomy. Although the serum total CK level remained within the reference range in the postoperative period, the serum CK-MB level soon became elevated above the reference range and decreased after elective right nephrectomy. Clinical evidence of tumor recurrence within the residual left hemikidney was not accompanied by a substantial increase in the serum total CK or serum CK-MB level, and on histologic examination, the tumor was found to contain only occasional rhabdomyomatous elements showing maturation consistent with previous chemotherapy.

In both of our cases, serum total CK and serum CK-MB levels were useful for determining the presence of residual tumor, and these results led us to speculate that total CK and especially the isoenzyme CK-MB are novel tumor markers for rhabdomyomatous Wilms tumor.

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