High Creatine Kinase MB Isoenzyme Activity Associated with a Rhabdomyosarcoma

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A 20-year-old man was found to have high plasma creatine kinase (EC 2.7.3.2) activity in association with a rhabdomyosarcoma of the prostate. There was a very high proportion of the MB isoenzyme. Clinical findings and changes in creatine kinase activity with time showed that this increase was not ascribable to myocardial disease. We believe that the high proportion of CK-MB, confirmed by a combination of electrophoretic and immunoinhibition studies, originated from the tumor.

Additional Keyphrases: cancer · source of plasma enzyme · isoenzymes

An increase in the MB isoenzyme of creatine kinase in the plasma is regarded as being a specific indicator of acute myocardial infarction (1). The recent demonstration of some variant creatine kinase isoenzymes has made interpretation of isoenzyme patterns more complex (2). In addition, the MB isoenzyme may increase slightly after exercise, without evidence of myocardial damage (3, 4).

We report a case of massive increase of the MB isoenzyme to previously unreported proportions, unaccompanied by evidence of myocardial damage. The patient had a rhabdomyosarcoma, and we suggest the tumor to be the source of the increased MB.

Materials and Methods

Plasma creatine kinase activity was measured with the "CK-NAC-activated" kit (Boehringer Mannheim GmbH, F.R.G.) in a Cobas Bio centrifugal analyzer. Residual creatine kinase-B subunit activity was measured with the "CK-MB (NAC-act)" kit (Boehringer Mannheim GmbH). For all samples, adenylate kinase (EC 2.7.4.3) activity was measured with a sample blank (no creatine phosphate substrate) and the appropriate correction made.

For electrophoretic separation of creatine kinase isoenzymes on agarose plates we used the Creatine Kinase Substrate Set (Corning Medical and Scientific, Palo Alto, CA 94306). Plates were scanned with a Cliniscan densitometer (Helena Labs., Beaumont, TX 77704).

Plasma lactate dehydrogenase (EC 1.1.1.27) and aspartate aminotransferase (EC 2.6.1.1) activities were measured with the "LDH UV opt. test" kit (Roche, Basle, Switzerland) and the "GOT opt. test" kit (Roche), in a Cobas Bio centrifugal analyzer.

Case Report

The patient, a 20-year-old white man, presented with acute retention of urine following a short history of abdominal discomfort and difficulty with micturition. Rectal examination showed an enlarged, hard prostate; a computer-assisted tomographic (CT) scan showed disseminated malignancy in the pelvic region.

A transurethral resection of the prostate was performed. Light-microscopic examination of the specimen obtained revealed elongated or stellate cells with large nuclei and little cytoplasm. In some areas the cells had eosinophilic cytoplasm in which cross-striations were found. Electron microscopy showed Z-line structures with the regular spacing pattern of muscle sarcomeres, and the pathologist concluded that the ultrastructure was that of a rhabdomyosarcoma, probably of the embryonal type, with marked variation in the level of cellular differentiation.

One course of cytotoxic chemotherapy was given, then the patient declined further active treatment. He presented again eight months after the initial diagnosis with symptoms indicating tumor recurrence. CT scan and isotopic bone scan demonstrated multiple metastases.

During this admission the patient complained of the sudden onset of discomfort in the left side of his chest. He was febrile and there was a loud pericardial rub. An electrocardiogram showed T-wave inversion in leads V1 and AVL and minor ST-T wave changes. During the next three weeks the T wave in V1 reverted, but the T wave inversion in AVL persisted. Results of an echocardiogram were normal and of viral serology negative. The chest discomfort rapidly settled. Cardiological opinion was that the incident was consistent with a tumor metastasis to the pericardium. A course of chemotherapy was given and the patient left the hospital.

When he first experienced the chest discomfort we measured the enzymes creatine kinase, aspartate aminotransferase, and lactate dehydrogenase in his plasma, and determined the creatine kinase isoenzyme pattern. Values for lactate dehydrogenase and aspartate aminotransferase were high: 1920 (normal reference interval 130–230) and 92 (6–42) U/L, respectively. Over the period of study the activity of both these enzymes remained above the reference interval, though activity was slowly declining. The initial creatine kinase activity was 608 U/L (reference interval 25–200) with 29% MB (MB, the myocardial-specific isoenzyme; the normal proportion is <4%). This inappropriately high value prompted us to serially estimate creatine kinase activity and isoenzymes. Myocardial infarction as the cause of the increased creatine kinase is excluded because of the extremely high proportion of MB (see below) and the persistence of the increase in the absence of any other signs of recurrent infarction.

Table 1 summarizes the results of the investigations performed. A five-day course of chemotherapy was commenced on 5 October, and the proportion of MB increased to over 60% and stayed high during the period of observation. The right-hand side of Table 1 lists proportions of M and B subunits calculated from the electrophoretic data. Being mindful of the possibility of variant isoenzymes, we also

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measured creatine kinase activity before and after inhibition of CK-M subunit activity (5). The percentage of activity remaining, which should represent the activity of the B subunits only, correlates well with the estimate of proportion of B subunits from the electrophoretic data \( r = 0.990, p < 0.01; y = 0.944x + 6.061; n = 5 \). To confirm the identity of this band with MB electrophoretic mobility, we pre-incubated samples with anti-M before electrophoresis. The MM and MB bands disappeared, replaced by a smear of fluorescence near the point of application. The BB band was unchanged. These results agree well with recent work of Stein and Bohner (6).

This implies that the band running at the position of MB on electrophoresis was in fact MB and not some variant isoenzyme of creatine kinase. It should be noted that the MB band migrated exactly the same distance and looked the same under ultraviolet light as it did in the routine quality-control sample (Isotrol; Sigma Chemical Co., St. Louis, MO 63178) and samples from patients with acute myocardial infarction. The high proportion of MB and the modest proportion of BB make it unlikely that this represents hybridization between creatine kinase-MM and -BB (2).

Discussion

The consensus is that 30% to 40% of myocardial creatine kinase is of the MB form and that this tissue has the highest MB content in normal human tissue (7). The highest value for MB in human plasma that we have found reported in the literature was 39%, from a patient with polymyositis (8). Thus our result is of particular interest in that it not only may be the highest value for plasma MB yet reported but also is higher than could be expected from any normal tissue.

There is evidence that creatine kinase BB may be produced by malignant tissues (9). There has recently been a report of MB production by tumor tissue (10), but it has been suggested that this was artefactual (2). Our data support the proposal that creatine kinase MB may indeed be a specific tumor product.

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References