Lactate dehydrogenase reflects the status of ultra-high-risk neuroblastoma in a child under treatment

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Abbreviation key

UHR	ultra-high-risk
LDH	lactate dehydrogenase
CT	computed tomography
HVA	homovanillic acid

UHR	ultra-high-risk
VMA	vanillylmandelic acid
MIBG	123I-metaiodobenzylguanidine
HDC	high-dose chemotherapy

To the Editor

Neuroblastoma is a well-recognized tumor in children but is sometimes highly aggressive. Morgenstern et al. reported an "ultra-high-risk" (UHR) subpopulation with inferior outcomes [1]. Several clinical factors, such as serum lactate dehydrogenase (LDH), are predictors of a poor prognosis [2] [34]. However, despite clinical experience, few studies have assessed the association between clinical factors and the disease status during treatment or the treatment response. We report a case of UHR neuroblastoma in which serum LDH concentrations were correlated best with the disease activity.

A 20-month-old Japanese girl presented to our hospital with poor vitality, tiredness, hematuria, and abdominal distension. There was no medical history. An examination showed the following: blood pressure, 139/59 mmHg; temperature, 38.0; pulse, 138/min; respiratory rate, 36/min; and oxygen saturation, 90% on ambient air. She was irritable and had a distended abdomen and an elastic mass. Laboratory studies showed the following: hemoglobin, 8.3 g/dL, LDH, 3117 IU/L, and ferritin, 117 ng/mL. She had no electrolyte abnormalities. An abdominal computed tomography (CT) scan showed an 11.1 × 8.6 × 10.3-cm^3 heterogeneous mass at the upper left kidney and thoracic ascites. Urine catecholamines were increased, with a homovanillic acid (HVA) concentration of 452 μg/mg creatinine and vanillylmandelic acid (VMA) concentration of 201 μg/mg creatinine. 123I-metaiodobenzylguanidine (MIBG) scintigraphy showed accumulation at the tumor site but no metastasis. A tumor biopsy showed an undifferentiated neuroblastoma with MYCN amplification and the diploid karyotype of chromosomes, and a bone marrow biopsy showed tumor invasion. We diagnosed high-risk neuroblastoma using the International Neuroblastoma Risk Group system. Previous reports suggested that this tumor was UHR [1]. We planned multiagent chemotherapy with five cycles of remission induction chemotherapy, tandem high-dose chemotherapy (HDC), surgery, and radiation therapy[5] [6]. After remission induction therapy, LDH concentrations increased from 262 IU/L to 1118 IU/L just before HDC. Contrast CT and MIBG scintigraphy showed that the tumor was reduced, and a bone marrow biopsy showed disappearance of the tumor. Urinary VMA and HVA concentrations were decreased. We administered HDC as planned because these results suggested that the chemotherapy was adequate. The maximum LDH concentration during the first HDC was 3264 IU/L, which was assumed to be the result of tumor disruption. By day 28 after the first HDC, the LDH concentration was decreased to 285 IU/L. Before the second HDC, urine VMA and HVA concentrations were decreased, but the LDH concentration was increased to 1155 IU/L. Enhanced CT did not show progressive disease. Therefore, we performed a second HDC course. The LDH concentration was decreased, and VMA and HVA concentrations remained decreased. On the day of surgery, 40 days after the second HDC, the LDH concentration spiked to 1558 U/L, but the tumor was small on CT, and we attempted tumor resection. Intraoperative findings showed that the tumor invaded the omentum, mesentery, pancreas, spleen, and left kidney. Ascitic fluid cytology was positive. Pediatric surgeons resected the tumor and left kidney, and the mesentery was resected to the extent that intestinal blood flow was unaffected. They also preserved the pancreas and spleen. Pathologically, the margins were positive. Therefore, we started radiotherapy immediately. Radiotherapy was started 10 days after surgery, and the LDH concentration was decreased to 525 U/L. During radiotherapy, we noticed abdominal distention and a high LDH concentration (1303 U/L). CT showed that the tumor was disseminated in the thoracic and abdominal cavities. The patient had treatment-resistant neuroblastoma. We decided to perform palliative treatment at the request of the patient's parents. The patient required continuous abdominal drainage owing to considerable abdominal distention caused by ascites effusion. Palliative chemotherapy was challenging to control the tumor, and bone marrow suppression made continuation difficult. The patient was discharged home and died 2 weeks later.

We describe an aggressive case of UHR neuroblastoma with serum LDH concentrations closely associated with

disease activity. Several clinical research groups have advocated risk stratification of high-risk neuroblastoma. They also attempted to recognize an UHR status to improve the prognosis and offer appropriate therapy for these patients. In addition to the initial status, treatment responsiveness is essential, but there are no established indicators. Tumor markers and imaging tests may be adequate to assess the response to therapy. At our facility, tumor marker results take longer than a week to obtain. Contrast-enhanced CT is invasive owing to radiation exposure and contrast agents, and MIBG scintigraphy is not available in some facilities. These imaging tests are often subjective and may require more work for accurate assessment. However, LDH is simple to measure and results are prompt. LDH is useful for reassessment because it reflects the disease activity and treatment responsiveness sensitively and accurately. LDH measurement is also helpful in areas with limited medical resources. In our case, elevated LDH concentrations may have triggered the addition of conventional chemotherapy to control the tumor before further HDC, contributing to the improved prognosis. We were not able to assess genomic factors; therefore, whether 1p loss, 11q loss, or 17q gain is relevant is unknown. However, elevated LDH concentrations after advanced treatment likely due to enlargement of the tumor may help rapid reconsideration of treatment strategies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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FIGURE LEGENDS

Figure 1

Trends in serum lactate dehydrogenase (LDH), urine homovanillic acid (HVA), and urine vanillylmandelic acid (VMA) concentrations versus the time since diagnosis. LDH concentrations were increased just before blood cells recovered, and the next high-dose chemotherapy (HDC) was started. LDH reflected disease activity better than VMA or HVA.

Figure 2

A: Computed tomography (CT) with contrast at diagnosis. B: 123I-metaiodobenzylguanidine (MIBG) scintigraphy at diagnosis. C: Contrast CT before HDC. The radiologist concluded that the interior was necrotic. D: CT just before surgery. E, F, G, H: CT showing disseminated recurrence during radiotherapy.

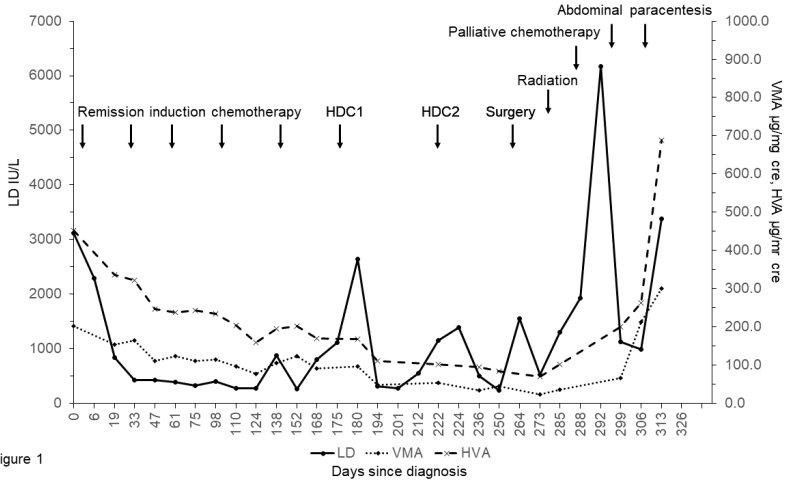

Figure 1

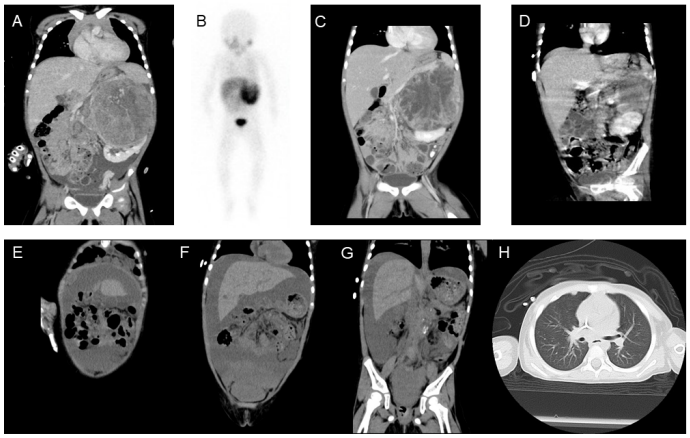

Figure 2