Prosthetic Valvular Hemolysis: a Potential Pitfall in the Routine Use of Serum Lactate Dehydrogenase as Tumor Marker in Patients with Germ Cell Testicular Tumors

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Some degree of intravascular hemolysis may be induced by heart valve replacement and is attributed to mechanical destruction of red blood cells, which are exposed to turbulent flow, high shear stresses and abnormal flow jets through the prosthetic valve. With the advent of modern mechanical prosthetic heart valves, clinically significant hemolysis has become relatively rare and occurs mainly with malfunctioning valves accompanied by paraprosthetic valvular regurgitation [1]. Elevated serum lactate dehydrogenase activity in patients with prosthetic heart valves is a well-documented phenomenon that reliably correlates with intravascular hemolysis [2]. Serum LDH and especially LDH₁ isoenzyme is a useful tumor marker associated with germ cell tumors and may be used for diagnosis, staging, monitoring of therapy, detection of relapse, and as an important prognostic factor [3].

We report a patient with past history of aortic valve replacement who was recently diagnosed with testicular seminoma. We emphasize the implications of chronically elevated serum LDH with high LDH₁/LDH₂ isoenzyme ratio due to prosthetic valvular hemolysis, which may considerably interfere with the usefulness of serum LDH as a tumor marker.

Patient Description
A 51 year old man was admitted for evaluation of a left testicular mass that he had noted several weeks earlier. Fourteen years prior to this admission he underwent aortic valve replacement and has been taking warfarin ever since. Previous cardiologic assessments documented a significant stable paraprosthetic valvular regurgitation. The patient had excellent performance status and did not experience any constitutional symptoms. Physical examination was unremarkable except for an enlarged firm irregular left testicle. Scrotal ultrasonography demonstrated variable sized hypoechoic hypervascular lesions. Serum alpha-fetoprotein and serum human chorionic gonadotropin were within the normal range. LDH level was 1446 U/L (normal 230–460 U/L). Chest and abdominopelvic computerized tomography scans showed no evidence of lymphadenopathy, pulmonary or visceral metastasis. Subsequently, the patient underwent an uneventful inguinal orchiectomy. Pathologic examination revealed pure seminoma diffusely involving the left testis, invading the rete testis and tunica albuginea without vascular or lymphatic invasion. The epididymis and the spermatic cord were not involved by the tumor. Post orchiectomy LDH levels declined slightly but remained consistently elevated, fluctuating between 1079 U/L, 1294 U/L and 1080 U/L on postoperative days 3, 7 and 35 respectively. All five LDH isoenzymes (LDH₁ through LDH₅) were elevated with high (0.95) LDH₁/LDH₂ ratio. Absolute LDH levels as well as failure of serum LDH to normalize following orchiectomy were suggestive of metastatic disease; nevertheless, careful revision of previous medical records revealed persistently elevated LDH levels as high as 1600 U/L dated back to 4 years before the diagnosis of germ cell tumors, which were attributed to prosthetic valve hemolysis and probably related to documented paraprosthetic regurgitation. After the equivocal implications of serum LDH in the current setting, inadequate clinical staging and lack of accurate monitoring ability were presented and explained to the patient and he elected to undergo surveillance. Presently he has no evidence of relapse.

Comment
Measurement of serum LDH and LDH₁ isoenzyme in particular is an important tool in the workup of patients with testicular cancer. Sixty-one percent of patients with GCT have raised LDH₁ at diagnosis. Overall, it is equally elevated in patients with seminoma and non-seminoma tumors but is encountered more frequently in low stage seminoma than low stage non-seminoma. LDH₁ level is correlated with the stage of GCT; it is integrated into the current staging system and is an established prognostic factor. Finally, since LDH₁ reflects tumor burden in patients with GCT, monitoring LDH₁ decay and normalization after orchiectomy or post-orchiectomy therapy is useful in patients managed by surveillance or during and after therapy and may detect tumor relapse or progression early [3].

Elevated marker levels, which do not necessarily indicate presence of active GCT disease, is a well-recognized pitfall in the routine clinical use of serum tumor markers. Many reports document false positive elevation of alpha-fetoprotein, human chorionic gonadotropin or both, as a consequence of non-GCT-related conditions, in patients with germ cell tumors [4]. Despite the significance of LDH as a

LDH = lactate dehydrogenase
GCT = germ cell tumor
GCT marker, its use and its relative non-specificity due to its widespread presence in normal and abnormal tissues, we did not locate any report of clinical confusion due to false positive elevation of LDH or LDH$_1$ in a patient with GCT. The present report describing a man with chronic elevation of LDH and LDH$_1$ due to intravascular hemolysis caused by a transplanted prosthetic aortic valve and a recently diagnosed testicular seminoma demonstrates the dilemmas posed by this confusing clinical concomitance. High serum LDH and LDH$_1$/LDH$_2$ ratio is a common finding both in intravascular hemolysis and germ cell tumor. According to the history of this patient, the significant elevation of LDH and LDH$_1$/LDH$_2$ ratio is probably due to prosthetic valvular hemolysis alone; however, a GCT component may still be pertinent, though we cannot differentiate between LDH contributed by the hemolysis and LDH contributed potentially by the GCT. This uncertainty interferes with the accuracy of TNMS staging. Based on LDH results alone, the clinical stage in the current case may shift from T$_1$N$_0$M$_0$S$_2$ (stage IA) to T$_1$N$_0$M$_0$S$_0$ (stage IA) if LDH is ascribed to a germ cell tumor source or to intravascular hemolysis respectively. It also excludes reliable assessment of response to orchietomy since normalization of LDH probably cannot be expected and there is no predictable LDH decay pattern. This primarily confusing issue was further obscured in the present case due to a moderate decay and fluctuations of LDH levels following orchietomy. This behavior cannot be interpreted with certainty in view of the previous prolonged stability of LDH level in this patient and the similar isoenzyme pattern of intravascular hemolysis and GCT marker. Nevertheless, LDH decline probably did not reflect decay of GCT marker but rather variations in the intensity of hemolysis.

In summary, this case report draws attention to an undocumented potential pitfall of a non-malignant source of chronic LDH elevation due to prosthetic valvular hemolysis. Elevated LDH levels and unpredictable decay pattern may interfere with the routine clinical use of LDH or LDH$_1$ as tumor markers in staging and monitoring and lead to overstaging and overtreatment in patients with germ cell tumor and transplanted heart valves.

References

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CASE COMMUNICATIONS

Loneliness is and always has been the central and inevitable experience of every man
Thomas Wolfe (1900-1938), American novelist

I never saw an ugly thing in my life: for let the form of an object be what it may; light, shade, and perspective will always make it beautiful.
John Constable (1776-1837), British landscape painter

Capsule
Furosemide is not effective in preventing and treating acute renal failure
Furosemide (frusemide) is not associated with any clinical benefits when used to prevent and treat acute renal failure in adults. In a meta-analysis of nine randomized trials, Ho and Sheridan investigated the potential beneficial and adverse effects of furosemide to prevent or treat acute renal failure. They found that in-hospital mortality, risk of requiring renal replacement therapy or dialysis, number of dialysis sessions required, and proportion of patients with persistent oliguria were not significantly different after treatment with furosemide. However, high doses of furosemide may be associated with an increased risk of ototoxicity.

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