Deep Hypoalbuminemia in Patients with Immunoglobulin Light Chain Amyloidosis: A Risk Factor for Vascular Thromboembolic Events or Only a Causal Link?

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Malignancies are associated with an increased risk of thromboembolic vascular events, that can involve both the venous and arterial sites. The venous thromboembolism (VTE) risk may increase in up to 13% in patients on active chemotherapy. VTE is known to be the second-leading cause of death in patients with malignancy. Moreover, when cancer-related deaths are excluded, VTE becomes the leading cause of death in cancer patients along with infection (9.2%) [1]. Given the reported thrombosis-related mortality rates along with high costs and extended hospitalisation, appropriate risk stratification and prevention of thrombosis need to be carefully determined in the setting of supportive cancer treatment.

Multiple myeloma (MM) is a clonal plasma cell disorder accounting for ~1% of all malignancies and >10% of hematological malignancies in the United States [2]. As well as other malignancies, MM is remained at an increased risk of VTE. The incidence of VTE in myeloma patients is mainly reported by studies in a therapy-related context. The VTE rate was found to be 12% in newly diagnosed MM patients treated with lenalidomide plus high-dose dexamethasone (no thromboprophylaxis), whereas it was only 2.27% in aspirin prophylaxis arm and 1.2% in low-molecular weight heparin (LMWH) arm [3].

International Staging System (ISS), utilizing a combination of serum β^2 microglobulin and serum albumin has been developed in 2005 [4]. ISS provides a reproduciple three-stage classification for myeloma patients. Low serum albumin levels (<3.5 g/dL) are associated with advanced disease status, high tumor burden and low median survival rates. However, to the best of our knowledge, hypoalbuminemia is not being described as a predictor of VTE in patients with MM.

Bever *et al*. have very recently reported that among the 824 available patients with immunoglobulin light chain (AL) amyloidosis, 7% of the patients had developed at least one VTE episode and 80% of them had vascular events within one year prior to or following diagnosis. The only significant risk factor for predicting VTE was reported as having a serum albumin level of <3 g/dL versus >4 g/dL. A subgroup analysis of 382 patients with nephrotic-range proteinuria (>3.5 g/day) associated with a higher VTE rate (9.7%). Interestingly, after the reanalysis, hypoalbuminemia did not reveal any significance with the development of VTE risk [5]. The association of serum albumin levels and risk of VTE is conflicting, whereas the ratio of proteinuria to serum albumin level is likely to be a stronger predictor of VTE in patients with nephrotic syndrome than serum albumin levels [6, 7].

The pathophysiology of VTE in AL amyloidosis is not exactly elucidated, but it seems to be multifactorial. In a recent retrospective analysis, nearly 60% of the patients complicated with VTE had primary renal involvement [5]. Alterations in plasma levels of pro- and anti-coagulant serum proteins are involved in the pathophysiology of VTE in nephrotic syndrome [8]. Similarly, the renal loss of antithrombin III [9], protein C, and/or protein S along with albumin should be expected in AL amyloidosis patients with renal involvement. One can speculate that the loss of natural anticoagulants in AL patients with renal involvement may explain, at least partly, why hypoalbuminemia is linked with higher rates of VTE in AL amyloidosis and not in MM. However, in contrast with this hypothesis, the impact of hypoalbuminemia for predicting VTE risk did not continue when the statistical analyses were repeated for only VTE patients with nephrotic range proteinuria [5].

In a large, retrospective study including 298 consecutive patients with nephrotic syndrome, not only the risk of VTE, but also the risk of arterial thrombotic

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events is remarkably elevated, especially within the first 6 months of diagnosis [6]. Antithrombin III deficiency is manifested primarily by recurrent VTE, whereas arterial thrombosis is reported less frequently [10]. Cardiac involvement in AL amyloidosis is also commonly associated with arterial thromboses [11]. In Bever *et al*.'s large scale cohort, a quarter of VTE patients had primary cardiac involvement [1]. Aspirin is classically more effective in preventing arterial thrombosis, but its efficacy in VTE remains controversial [12, 13]. Bagratuni *et al*. had reported that among 200 unselected MM patients who were treated with a lenalidomide-based regimen, all VTEs were detected in patients under aspirin prophylaxis [14]. Similarly, in a large real-life observational study including 524 MM patients, VTE episodes were observed 7% on aspirin, whereas only 3% on LMWH, and none on vitamin K antagonists [15].

In conclusion, hypoalbuminemia as a promising risk factor of VTE in AL amyloidosis, needs to be further evaluated with prospective studies. Not only VTE episodes, but also arterial vascular thrombotic events and cardiac involvement should be carefully evaluated. The individual patient is at the center and optimal patient outcome should be its goal.

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