L-Asparaginase induced thrombosis in acute lymphoblastic leukemia

Sir,

I read with interest the report by Dubashi and Jain on a 16-year-old patient with acute lymphoblastic leukemia (ALL), presenting with cortical venous thrombosis (CVT) after L-asparaginase therapy.[1] Authors indeed have added to the body of literature on thrombosis secondary to L-asparaginase in leukemia patients form India. We believe that the following comments and observations will be noteworthy in this regard.

As the authors have pointed out, the risk of symptomatic thrombosis in childhood acute leukemia is approximately 5%.[2] However, asymptomatic and symptomatic thrombosis may be observed in as many 73% of the ALL patients with central lines and treated with chemotherapy.[2] Akin to the reported patient, most patients are diagnosed with thrombosis during induction therapy.[3] It would be useful to know if the index patient had any central lines, co-morbidities, or inter-current illnesses. Although central lines are not directly related to CVT, they often cause other central venous thrombosis. [2,4]

As mentioned by the authors, the patient also received steroids during the induction phase. Steroids are also known to modulate the coagulation system and increase the risk of thrombosis.[4] Both the drugs may act in synchrony with each other to increase thrombotic risk. The role of steroids in causing CVT is unclear however they may act in synergy with L-asparaginase to increase the risk of thrombosis by up to 6 to 8 fold.[2,4]

Also, data on leukemia subtype, cytogenetics, and any molecular studies done in the index patient will be extremely helpful in understanding the thrombotic risk of the patient better.[2,4] This is especially more important since sub-type of leukemia and prothrombotic tendencies (for instance: Factor V leiden mutation, prothombin gene G20210A mutation, plasminogen activator inhibitor gene, methylene tetrahydrofolate reductase mutations, factor VIII levels and other procoagulant phenotypes and genotypes) may modify the risk of clotting.[4] Additionally, use of more contemporary risk adapted rather than MCP841 protocol might have modulated the patient's risk of experiencing a thrombotic event. The protocol used for therapy is important since the doses of steroids and L-asparaginase as well as their timing vary by protocols. Moreover the type and formulation of these drugs may also impact the thrombotic risk.[2,4]

In the absence of a central database or registry, in an attempt to identify the incidence of L-asparaginase related thrombotic events from India, a systematic search was conducted to find out all cases of L-asparaginase induced thrombosis from India using a combination of MESH terms to determine relevant papers without age, language, or date restriction. Two hundred and five articles were screened. Only one other case series of two patients (13- and 10-year olds) with ALL and mixed phenotype leukemia with sinus-venous thrombosis have been reported.[3] The impact on outcome is unclear since one of these patients survived while the other one died. Further, other articles form India on outcome of childhood ALL were screened to identify additional cases.[5] No additional data on thrombotic complication of ALL form India are available and published.

Almost 10,000 new cases of childhood ALL are likely diagnosed in India each year. The L-asparaginase and steroids are the backbones of therapy for childhood ALL.[5] Thrombosis is one of the most well-recognized complications of L-asparaginase therapy, having potentially disastrous consequences.[2] Even with a 5% incidence, over 500 new cases of thrombotic complications should be reported each year. As observed by us, there is a stark paucity of reported literature on thrombotic complications in ALL from India, with only three cases of post-asparaginase thrombosis reported so far.[1,3]

Very few published papers from India on this topic indicate the need of more active surveillance and a very high index of suspicion as well as better reporting of adverse events during therapy. With improving survival outcome of ALL, the focus also needs to be on the identification of morbidities, especially drug-induced toxicities.

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