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The role of hypoxia-inducible factor-1 alpha in TEMPI syndrome

Sir,

Two recent reports in *The New England Journal of Medicine* on a newly described syndrome, namely TEMPI syndrome (telangiectasia, erythrocytosis, monoclonal paraprotein, paranephric fluid collections, intrapulmonary shunting) are fascinating [1, 2], considering the number of cases where the radiological finding of perinephric fluid collections are not investigated further [3] or the concomitant laboratory finding of a paraprotein is dismissed as another case of monoclonal gammopathy of undetermined significance (MGUS). Sykes *et al.* [2] hypothesize that the IgG paraprotein in TEMPI syndrome may be pathogenic due to the resolution of most clinical features after a trial with the proteasome inhibitor, bortezomib. But, as bortezomib also affects the function of hypoxia-inducible factor-1 alpha (Hif-1α) and down-stream transcription of vascular endothelial growth factor (VEGF) [4], inhibition of Hif-1α would also explain the resolution of the symptoms seen in the patient described by Sykes *et al.*

Expression of Hif-1α and Hif-1α messenger RNA has been detected in all human tissues [5]. Intratumoral hypoxia is known to induce Hif-1α expression that increases VEGF and angiogenesis, but growth factors and loss-of-function mutations in von Hippel Lindau gene and p53 also induce Hif-1α expression (and possibly development of telangiectasias and erythrocytosis) [6]. Zhang *et al.* [7] showed that even under normoxic conditions, the oncogenic c-Myc/Hif-1α pathway modulates multiple myeloma cell production and mediates production and secretion of VEGF. Bortezomib was also shown to decrease both c-Myc and Hif-1α levels. Specific inhibitors of Hif-1α may therefore reverse most of the pathological manifestations of TEMPI syndrome.

Conflict of interest statement. None declared.

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