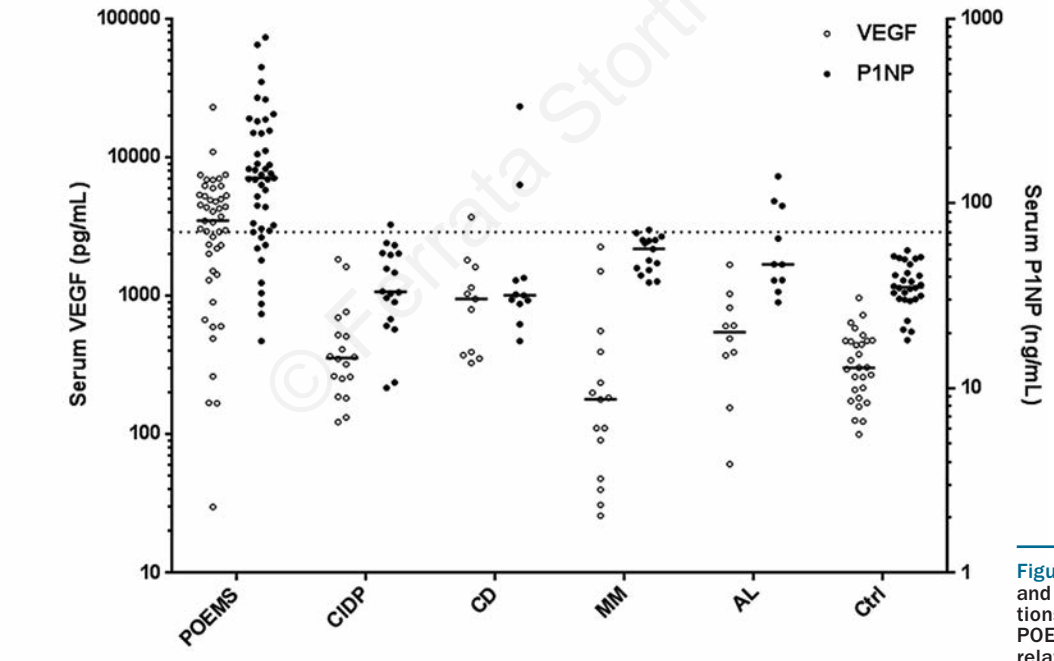
Markedly elevated serum total N-terminal propeptide of type I collagen is a novel marker for the diagnosis and follow up of patients with POEMS syndrome

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) is a rare plasma-cell dyscrasia.[1,2] Its diagnosis relies on both clinical and laboratory features, and osteosclerosis is a major diagnostic criterion.[3] Although conventional imaging methods, including X-ray and computed tomography, can be informative, these techniques are neither sensitive nor specific to detect the sclerotic changes.[4-6] N-terminal propeptide of type I collagen (P1NP) is the cleavage product of type I collagen, which constitutes 90% of the bone protein. Because its intraindividual variability is low, sample stability is robust, and high-throughput measurements are possible, serum P1NP is a newly emergent marker of bone formation, and has shown its clinical values in the detection of osteosclerotic metastases in cancer patients.[7] Therefore, serum P1NP might also be useful to reflect the osteosclerosis in POEMS syndrome. Herein, we evaluated the diagnostic significance of serum P1NP in 45 newly diagnosed patients with POEMS syndrome (*Online Supplementary Table S1*). Healthy volunteers (n=28) and patients with disease manifestations similar to those of POEMS syndrome, including chronic inflammatory demyelinating polyneuropathy (CIDP) (n=18), Castleman disease (CD) (n=11), multiple myeloma (MM) (n=15) and primary light-chain amyloidosis (AL) (n=10), were used as normal and disease controls, respectively.

The serum levels of total P1NP in patients with POEMS syndrome were markedly elevated (median 137 ng/mL, range 18-792 ng/mL) compared with those of the normal subjects (median 35 ng/mL; $P<0.001$), and patients with CIDP (median 33 ng/mL; $P<0.001$), CD (median 32 ng/mL; $P=0.001$), or other plasma-cell dyscrasias (MM and AL) (median 49 ng/mL; $P<0.001$) (Figure 1). Using a receiver operating characteristic (ROC) analysis, the best P1NP cut off for POEMS diagnosis was 70 ng/mL, with a specificity of 91.5% and a sensitivity of 80%. The area under the curve (AUC) was 0.87 (95% confidence interval (CI): 0.78-0.95; $P<0.001$). The diagnostic performance of serum VEGF, a well-established biomarker for POEMS syndrome,[8] was also analyzed in these patients. The AUC was 0.89 (95%CI: 0.80-0.95; $P<0.001$), and the best cut off was 1920 pg/mL (specificity 97.6%, sensitivity 73.3%). No statistical difference was observed between these two markers for their diagnostic performance (z statistic = 0.40; $P=0.687$). Moreover, fulfillment of either serum total P1NP more than 70 ng/mL or serum VEGF more than 1920 pg/mL could dramatically improve the



Diagnosis	N=45	N=18	N=11	N=15	N=10	N=28
VEGF (pg/mL)						
Median	3476**	356	949	179	549	304
Range	30-22993	123-1831	328-3697	26-2261	61-1677	100-966
P1NP (ng/mL)						
Median	137**	33	32	57	47	35
Range	18-792	10-77	18-335	37-72	29-140	18-56

Figure 1. Serum VEGF and total P1NP distributions in patients with POEMS syndrome and related disorders. The horizontal line represents the optimal cut-off value for serum total P1NP (70 ng/mL) supporting a diagnosis of POEMS syndrome. CIDP: chronic inflammatory demyelinating polyneuropathy; CD: Castleman disease; MM: multiple myeloma; AL: primary light-chain amyloidosis; Ctrl: normal control. $**P<0.001$.

Table 1. Serial serum VEGF and total P1NP levels in relapsed patients.

Pt. No	Cytokine	Diagnosis	1st Remission	Relapse	2nd Remission	Primary therapy	Remission period (months)	Reason for next therapy	Next therapy
1	VEGF P1NP	861 36	407 54	2706 114	NA	ASCT	34	Worsening skin and new edema	LDex
2	VEGF P1NP	5324 183	367 65	2974 285	790 133	MDex	36	New adenopathy and edema	LDex
3	VEGF P1NP	6471 157	1102 59	1866 198	1129 102	MDex	38	New ascites and edema	LDex
4	VEGF P1NP	2537 108	981 54	2130 386	2230 63	MDex	43	Worsening PN (2 new points in ONLS score)	LDex
5	VEGF P1NP	2678 841	615 112	4439 315	NA	MDex	29	New ascites and edema	LDex
6	VEGF P1NP	6201 146	737 71	1122 120	1032 69	MDex	48	New edema	LDex

Pt No.: patient number; VEGF: vascular endothelial growth factor; P1NP: N-terminal propeptide of type I collagen; NA: not available; ASCT: autologous stem-cell transplantation; MDex: melphalan and dexamethasone; LDex: lenalidomide and dexamethasone; PN: peripheral neuropathy; ONLS: Overall Neuropathy Limitation Scale.

diagnostic sensitivity to 91.1%, while slightly decreasing the specificity to 90.2%.

As serum total P1NP is a marker of bone formation, we compared its level in POEMS syndrome patients with (n=17) and without (n=28) bone changes. Patients with bone changes were further subdivided into those with sclerotic changes only (n=11) and those with mixed sclerotic and lytic components (n=6). No patient only had lytic changes. There was no statistical difference between patients with and without bone changes (median 143 *vs.* 136 ng/mL; *P*=0.519) (*Online Supplementary Figure S1*).

We also measured the serial changes of serum VEGF and total P1NP in 6 patients with relapsed disease courses (Table 1). For the initial therapy, 5 of them received a regimen of melphalan and dexamethasone and one underwent autologous stem cell transplantation. Serum levels of total P1NP were significantly reduced after treatment and reached the normal base-line level in all but one patient. The reduction in serum markers was associated with improvements in clinical symptoms. After a certain period of remission (median 37 months, range 29-48 months), these patients developed new symptoms, as well as elevated serum VEGF and total P1NP levels. All of them received further therapy (lenalidomide and dexamethasone) and 4 patients achieved a second clinical remission during their follow up, when they also showed reduced serum VEGF and total P1NP levels. The remaining 2 patients are still under treatment.

Our data indicate that serum total P1NP was markedly elevated in patients with POEMS syndrome, and had excellent diagnostic performance, which was not inferior to VEGF. Moreover, when these two biomarkers were used in parallel, the diagnosis of POEMS syndrome became more practical. These observations support the use of serum total P1NP, along with serum VEGF, as a diagnostic criterion for POEMS. With the availability of these biomarkers, identification of patients in infancy becomes possible, and may markedly shorten the diagnostic delay and benefit patients.

Interestingly, the serum total P1NP levels did not differ in patients with and without sclerotic changes. Regardless of the incomplete recognition of lesions by inexperienced radiologists in developing countries, we wonder whether there are much smaller or more extensive changes in these imaging-negative patients. These changes may be below the detection sensitivity of conventional imaging techniques. Therefore, bone involvement may actually be more common than previously thought and could be a defining feature of POEMS syndrome.

Another important application of serum total P1NP might be its role in disease monitoring of POEMS syndrome. Currently, VEGF is always measured before and after treatment. As far as the osteosclerosis is concerned, there is no easily applicable criterion to evaluate the treatment response. Good correlations were observed for serum total P1NP levels with both clinical symptoms and serum VEGF levels in patients who experienced relapse. Theoretically, it may also have potential value for patients receiving radiation therapies for bone lesions, as serum P1NP is a marker of bone formation. In patients with ameliorated clinical symptoms and reduced serum total P1NP levels, stable remission can be expected. However, for those with sustained high levels of serum total P1NP, salvage therapy may need to be considered carefully. Certainly, its clinical value requires further investigation.

In summary, we have demonstrated, for the first time, the performance of serum total P1NP, a marker of bone formation, in the diagnosis and follow up of POEMS syndrome.

Chen Wang,[1] Ying-Lei Zhou,[1]* Hao Cai,[1] Xin-Qi Cheng,[2] Wei Zhang,[1] Wen-Ying Kang,[1] Xu-Zhen Qin,[2] Ming-Hui Duan,[1] Hui-Juan Han,[2] Xin-Xin Cao,[1] Dao-Bin Zhou,[1] and Jian Li[1]*

**CW and Y-LZ contributed equally to this work.*

[1]Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing; [2]Department of Clinical Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Correspondence: lijian@pumch.cn
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