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Case Report

Heavy metals intoxication in a patient with POEMS-like symptoms: a case report

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Abstract: Background: POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) is a kind of plasma cell disease with complex clinical manifestations involving multiple systems. Metal poisonings through a mucocutaneous are rare in clinic and reported less in the literature. People may exposure to toxic metals through air, food, water, or inappropriate use of drugs. Acute or chronic poisonings can lead to various toxic effects on body tissues and organs. Both POEMS syndrome and heavy metal intoxication are uncommon with multifarious and nonspecific clinical manifestations. Here we describe a case of a 54-year-old man with polyarticular pain and IgA lambda type monoclonal protein in his serum. The diagnosis was confirmed by heavy metals testing in his urine and the herbal mixtures he took. This is the first available report of arsenic and mercury intoxication mimicking POEMS syndrome.

Keywords: POEMS syndrome, heavy metals poisoning, arsenic poisoning, mercury poisoning

Introduction

The POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) syndrome is a rare paraneoplastic syndrome due to an underlying plasma cell disorder, which was first describe in 1980 by Bardwick [1]. The diagnosis of this syndrome is based on two mandatory major criteria: (polyneuropathy and monoclonal plasma proliferative disorder), one major criteria (sclerotic bone lesions, elevated vascular endothelial growth factor (VEGF), and Castleman's disease), and one of the six minor criteria (organomegaly, extravascular volume overload, endocrinopathy, skin changes papilledema, and thrombocytosis or polycythemia) [2, 3]. The diagnosis of this syndrome is challenging due to its low prevalence, multiorgan involvement and diverse clinical manifestations. Treatments of POEMS syndrome include localized radiotherapy, autologous stem cell transplant and chemotherapy [4, 5]. Glucocorticoids and thalidomide are proved to be effective for its treatment [6, 7]. It is known that heavy metals are natural components of the earth's crust, which are the oldest toxins. Potential exposures to heavy metals include contaminated food, industrial processes, commercial products, and herbal products [8]. Heavy metals, especially arsenic and mercury, are common constituent or contaminant of many nonwestern traditional medicine remedies. Arsenic or mercury intoxication occurs sporadically by use of Chinese folk prescriptions in China [9, 10]. Arsenic absorption is from the gastrointestinal tract, skin contact and inhalation. Arsenic toxicity is related to the dysfunctions of numerous vital enzymes, which cause dysfuctions of many tissues and organs including lung, heart, and so on [11]. In acute arsenic poisoning, the clinical features initially are gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain [12, 13]. In chronic arsenic exposure, a wide range of clinical features can be seen [14], such as dermatologic changes [15], peripheral neuropathy [16], and malignancies [17]. Organic mercury is easily absorbed from the gastrointestinal tract and distributed throughout the body. Mercury preferentially accumulates in the kidneys and exerts deleterious effects especially in the proximal tubules. Mercury poisoning can also lead

to chronic injuries to peripheral nerves, and impairment of liver function [11, 18]. For the clinic, it is difficult to make an early diagnosis due to the unknowingly exposures of heavy metals, especially for sporadic cases. The use of the corresponding antidote is helpful for treatment. Here, we present an atypical case characterized by POEMS-like symptoms but diagnosed as arsenic and mercury intoxication.

Case presentation

A 54-year-old rural man was admitted to the Department of Rheumatology and Immunology of Tongji Hospital with 20 days of increasingly and extremely polyarticular pain. He started to suffer from joints pain of shoulder, hips, and knee without obvious causes, which seriously affected his work and life. At the time of admission, he had mild diarrhea, without fever, cold, cough, nor sputum. He was a previously healthy man with no other chronic diseases. He had no trauma and drug abuse before. There was nothing remarkable about his family history. Physically, he had non-specific but obvious hyperpigmentation in both lower limbs. His liver and spleen were not palpable under the ribs. There was no edema on his face and lower limbs. Meanwhile, nervous system examinations were also negative. Blood tests showed that his white blood cell count was 8.25×10^9/L, with a hemoglobin concentration of 150 g/L, and a platelet count of 205×10^9/L. His liver functions showed that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were normal; blood albumin was 45.9 g/L; globulin was 26.5 g/L; alkaline phosphatase (ALP) was 86 U/L; creatine kinase (CK) was 486 U/L (reference range: ≤190U/L); lactate dehydrogenase (LDH) was 223 U/L. His creatinine was 56 μmol/L; glomerular filtration rate (eGFR) was 111.5 ml/min/1.73 m^2; and electrolytes were normal, while routine urine examination showed that urine protein was ++, 24 hours urine total protein was 590.9 mg (reference range: ≤140 mg/24 h), and 24 hours urine albumin was 413.3 mg (reference range: ≤30 mg/24 h). The thyroid and parathyroid functions were also measured, both were within the normal ranges. His cranial computed tomography (CT) and cardiac Doppler ultrasound showed no abnormalities. The whole abdomen CT showed that the size and shape of liver, spleen, and kidney were normal. The ileum and right colon intestinal cavity were inflated and expanded, and there were no enlarged lymph nodes in the retroperitoneum and pelvic wall. Doppler ultrasound of the arteriovenous blood vessels of the lower extremities showed no abnormalities in the venous blood vessels and multiple micro atherosclerotic plaques in the arteries.

The patient complained that he kept suffering from joints pain, but the above-mentioned vascular lesions were obviously not enough to cause the patient's pain of this degree, so we performed a rheumatic immune system laboratory examination. All his autoantibodies were negative, including the anti-nuclear antibodies (ANAs), anti-cyclic citrullinated peptide antibody (CCP), anti-rheumatoid factor antibody (RF), anti-keratin antibody (AKA), anti-neutrophils cytoplasm antibodies (ANCA), antiphospholipid antibody (APL), and anti-α-fodrin antibody. HLA-B27 was also negative. A quantitative analysis of the immunoglobulins in his blood showed that he has hyper-IgA of 4.64 g/L (reference range: 0.7-4 g/L). Serum immunofixation electrophoresis showed that there was IgA lambda type monoclonal protein in his blood samples (**Figure 1A**). The bone marrow cytomorphologic and histologic examination revealed high proportion of red blood cell system (**Figure 1C** and **1D**), and bone marrow flow immunophenotyping test confirmed 0.04% monoclonal abnormal plasma cells. Karyotype analysis of bone marrow was 46, XY [20]. Based on these findings, a diagnosis of a plasma cell disease, such as POEMS syndrome, monoclonal gammopathy of undetermined significance (MGUS) or monoclonal gammopathy of renal significance (MGRS), was considered. The patient then received further examinations. Sex hormone examinations were abnormal and an increased hormone level of luteinizing hormone (9.65 mIU/mL, reference range: 1.24-8.62 mIU/mL) and prolactin (60.18 ng/mL, reference range: 2.64-13.13 ng/mL) were discovered. Serum VEGF level was 167.74 pg/mL (reference range: 0-142 pg/mL). The electromyogram (EMG), bone mineral density of lumbar spine and hip, bone imaging of whole body, positron emission tomography (PET-CT) scan were all normal (**Figure 2A-C**). Considering all the findings together, we reluctantly diagnosed it as POEMS syndrome. Thus, we used

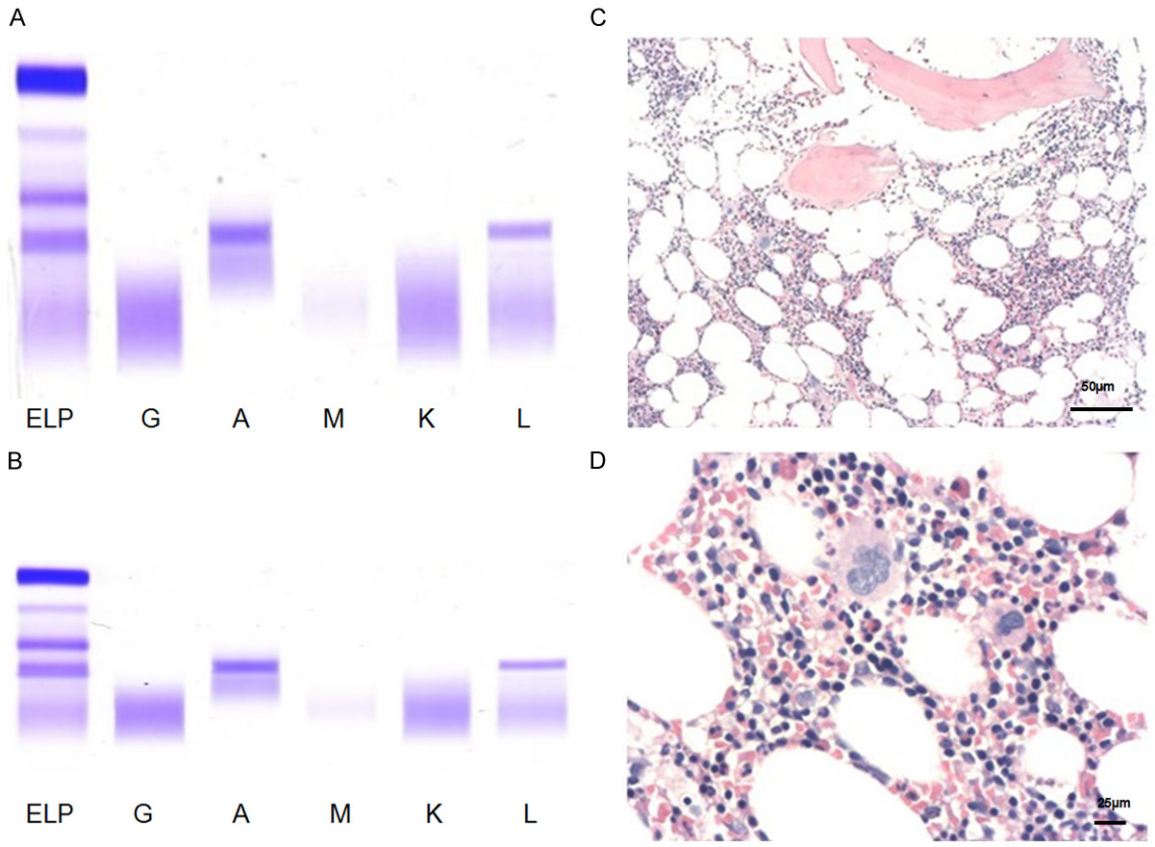

Figure 1. Serum with immune fixation electrophoresis and bone marrow biopsy. (A) There was IgA lambda type monoclonal immunoglobulin in serum of the patient on admission. (B) After 3 courses of DMPS treatment, there was still IgA Lamda type monoclonal immunoglobulin in serum of the patient (ELP: electrophoresis, G: IgG, A: IgA, M: IgM, K: kappa light chain, L: Lamda light chain, DMPS: sodium dimercaptosulphonate). (C, D) The bone marrow histologic examination (original magnification ×100 in C and ×400 in D).

glucocorticoids and thalidomide for empiric therapy. However, the treatment had to be interrupted at the first week, because there was no relief of the patient's unbearable pain. Meanwhile, many powerful painkillers were used. As shown in **Figure 3A**, anti-inflammatory analgesics (Loxoprofen sodium tablets, Celebrex, Etoricoxib tablets), Lyrica and sedative hypnotics (Estazolam tablets, Diazepam injection, Phenobarbital sodium for injection) were ineffective; opioid analgesics (Bucinnazine hydrochloride injection, Dezocine injection, Duloxetine hydrochloride enteric capsules) had poor efficacy. During the treatment of the disease, what puzzled us most was the severe joints pain of the patient. Then we sent the patient's samples of blood for heavy mental testing on the day 6 of the patient's hospitalization. The results showed that blood arsenic level was 11.36 μg/L (reference range: 0-12 μg/L), which was close to the maximum reference value of human blood heavy metal content (**Figure 3B**).

On follow-up medical history, the patient described he took brown pills of unknown folk prescriptions for 2 months, due to skin lesions on his legs. We decided to send blood and urine of this patient, as well as herbal mixture he took for testing again on the day 12 of the patient's hospitalization. To facilitate testing, we tried to dissolve the brown pills in normal saline and found that it did not dissolve in water. So, we took two pills, ground them, diluted them with normal saline, and sent the solid-liquid mixtures for testing. Surprisingly, excessive amounts of arsenic and mercury were detected in the patient's urine. As shown in **Figure 3B**, the amount of urine arsenic was 74.4 μg/L (reference range: 0-35 μg/L), urine mercury was 87.9 μg/L (reference range: 0-9 μg/L, >16 years old), and the heavy metal con-

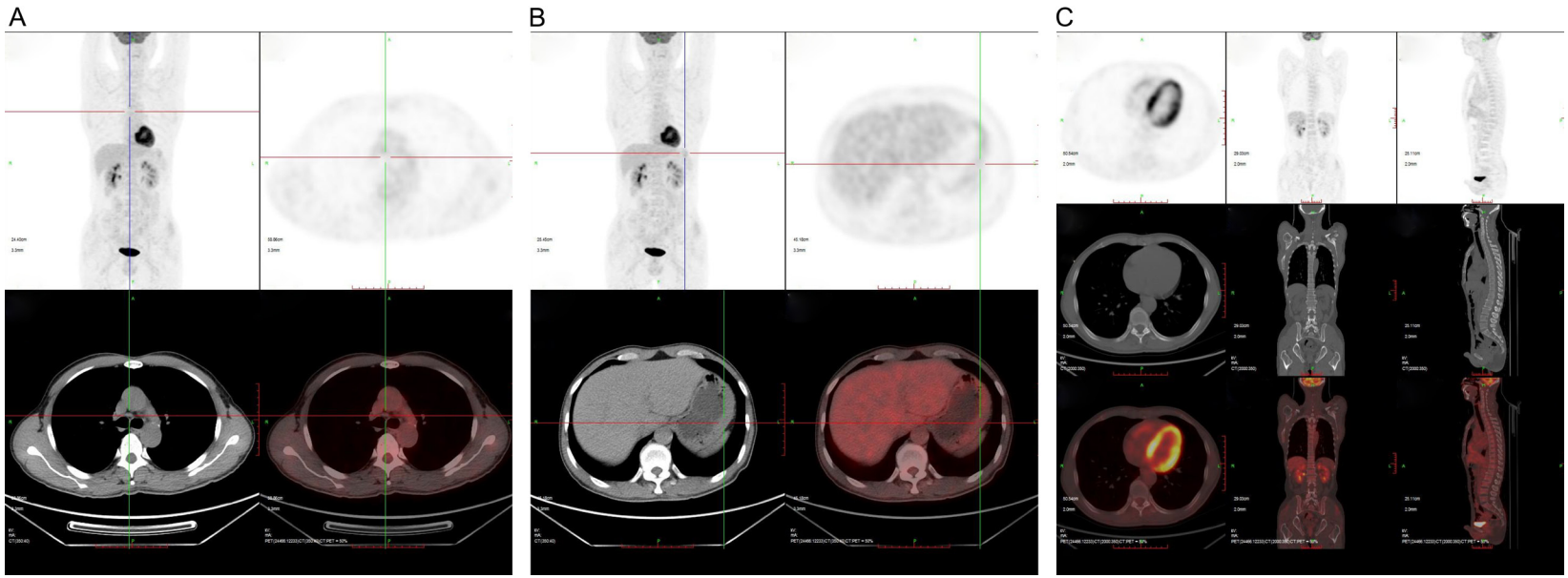

Figure 2. PET-CT images of this patient. (A) The patient had no hepatosplenomegaly in PET-CT. (B) No enlarged lymph nodes were seen in this patient. (C) The patient had no osteosclerotic lesions as well.

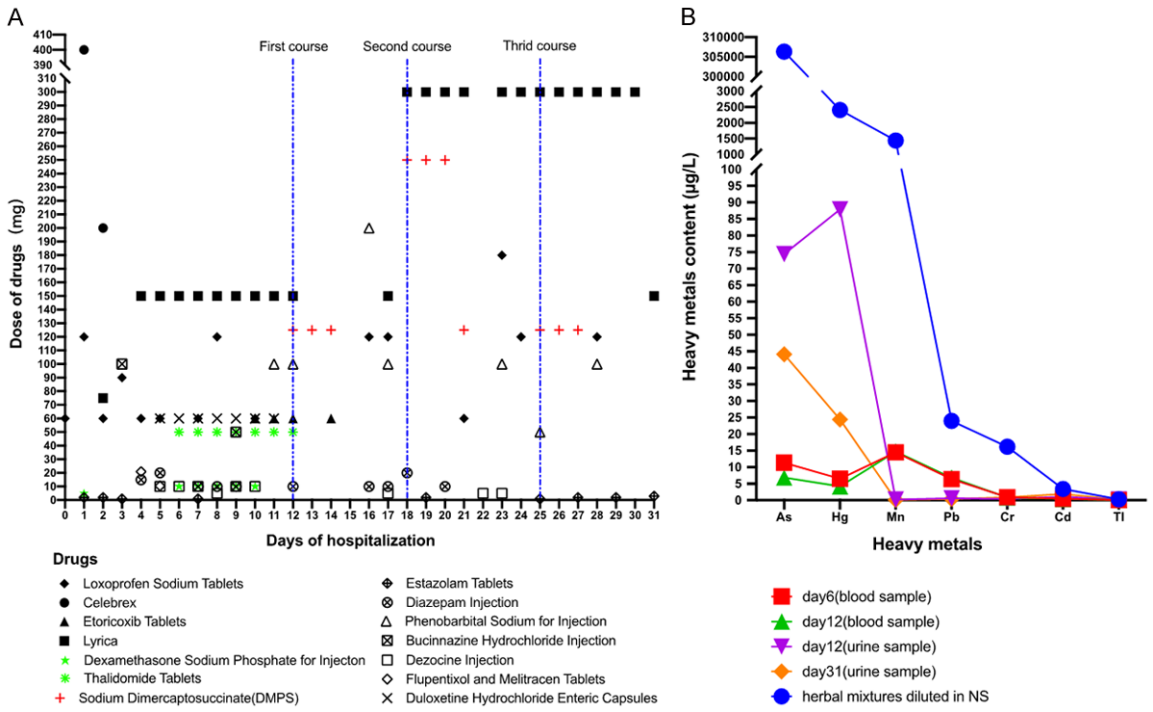

Figure 3. The treatment process and heavy metals content of the patient. (A) The whole treatment process of the patient. Treatment of DMPS was performed on day 12, day 18 and day 25 of the patient's hospitalization. (B) Heavy metals content in blood and (or) urine samples on day 6, day 12, and day 31 of the patient's hospitalization. The herbal mixtures were grounded and diluted with NS into solid-liquid mixtures for testing. NS: normal saline.

tent in the herbal mixture was unexpectedly high with arsenic 306354.2 μg/L, and mercury 2404.8 μg/L. Therefore, a 3-course chelation therapy with sodium dimercaptosulphonate (DMPS) was performed on day 12, day 18 and day 25 of the patient's hospitalization. The frequency of pain episodes and analgesics were significantly reduced (**Figure 3A**). We retested the patient's urine on the day 31 of the patient's hospitalization. The result showed that the arsenic and mercury level in urine significantly decreased to 44.1 μg/L and 24.4 μg/L, respectively. Because of the improvement of his symptoms and his family situation, we approved his discharge on day 31 of the patient's hospitalization and advised him to take regular medication at home. During the treatment, we monitored the patient's urine protein and renal function at the same time. Unlike the rapid decline of arsenic and mercury in the urine, the patient's protein in urine and renal function did not change much from admission to discharge. Serum immunofixation electrophoresis showed that there was still IgA lambda type monoclonal protein in his blood when the patient was discharged from the hospital (**Figure 1B**). In the following follow-up, the patient did not complain of pain and discomfort.

Discussion

POEMS syndrome is a rare disease, which has complex clinical manifestations involving multiple systems. Same as other plasma cell diseases, it affects people with age ranging from 40 to 60 years [19-21]. Polyneuropathy was observed in all patients, and it was usually the most important clinical manifestation [21-23]. According to a retrospective cohort study from the Mayo Clinic, 88% of patients had monoclonal protein in serum or urine samples, and the type of light chain was always lambda type [21, 24]. In patients with POEMS syndrome, VEGF levels were usually at least 3-4 times higher than the upper limit of normal, usually 5-10 times higher [21, 25]. Endocrinopathy was observed in 67-84% of the patients including hypogonadism, adrenal insufficiency, hyperprolactinemia, hypothyroidism, and diabetes mellitus [23]. The period between onset of symptoms and diagnosis of POEMS was reported to

be 13-18 months [21, 22]. Atypical POEMS syndrome was reported without polyneuropathy or elevation of VEGF in atypical cases [26, 27].

In this case report, the patient showed unbearable pain of multi-joints, accompanied by IgA lambda type M protein, proteinuria, hyperprolactinemia, skin pigmentation, mild elevation of VEGF, without polyneuropathy. Strictly, these were not typical symptoms of POEMS syndrome. We once considered it as POEMS syndrome, in which the patient's intense unrelieved pain and the lambda type monoclonal protein in serum of the patient played key roles. Although MGUS can also present as pure M-proteinemia, it is usually accompanied by abnormalities in bone marrow karyotypes [28]. The patient had proteinuria at admission, and the urine protein was still positive in repeated reexaminations after admission, but the patient's renal function and eGFR did not show any abnormality, which didn't support MGRS [29, 30]. Considering the POEMS-like symptoms and proteinuria of the patient, we used glucocorticoids and thalidomide for empirical treatment.

However, there are still doubts in this case. First, whether POEMS or MGUS, pain are generally a slow process, while severe and intense pain is usually accompanied by involvement of other system symptoms. It was clear that the patient's pain was an acute onset process, and that severe and intense pain occurred without lesion of a muscle, nerve, or bone. Second, we found protein in urine of this patient, which usually suggested that kidney lesion was considerable. What caused proteinuria? In patients with POEMS syndrome, serum creatinine levels are normal in most cases [3]. However, in a retrospective study of 299 patients with POEMS syndrome from China, 67 had renal impairment, mostly of moderate degree. Accordingly, arsenic and mercury poisoning are often associated with kidney damage [31, 32]. Arsenic poisoning can result in proteinuria, hematuria, acute tubular necrosis, and anuria [31]. Mercury poisoning has been reported to be associated with nephrotic syndrome [31, 33]. Given the short-term exposure to large doses of exogenous substances, we collected herbal history of the patient, and toxicologic analyses confirmed the diagnosis finally. The unresolved pain of the patient was relieved after effective antidote. Due to the diagnosis of arsenic and mercury poisoning was clear, and the treatment was effective, further examinations for precise clinical diagnosis of proteinuria were not performed. Likewise, the relationship between arsenic and mercury poisoning and monoclonal protein or MRUS remains ambiguous.

To our knowledge, this is the first study worldwide to report arsenic and mercury intoxication in the patient with POEMS-like symptoms. In fact, the treatment of heavy metal poisoning is not difficult, but it is difficult in the diagnosis. It is crucial for the diagnosis whether we consider the possibility of heavy metal poisoning in the comprehensive assessment of the patient. This is especially important for occasional cases of heavy metal poisoning, in which the patient is often unknowingly exposed to food, drugs, or water containing heavy metals. Therefore, detailed history collection and physical examination are very necessary. Early diagnosis and treatment are extremely important to reduce multiple organ damage caused by heavy metal poisoning and the prognosis of patients. It's worth noting that arsenic and mercury are eliminated quickly from the blood, therefore urine tests are more reliable than blood tests, except in some cases of acute arsenic and mercury poisoning. The diagnosis of arsenic and mercury toxicity was delayed in our case, because of improper selection of samples for heavy metal testing.

Conclusion

POEMS syndrome is an uncommon paraneoplastic syndrome, with diverse clinical and pathological manifestations. It can guide us in differentiating POEMS syndrome from other diseases by detailed medical history collection, careful physical examination, and thorough diagnostic evaluation. Especially for patients with high-risk factors of heavy metal poisoning (rural areas people with a medication history of folk prescription), the detection of heavy metal content in urine should be tested, which can help for a rapid diagnosis.

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Disclosure of conflict of interest

None.

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References

[1] Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway GD and Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. Medicine (Baltimore) 1980; 59: 311-322.

[2] Khouri J, Nakashima M and Wong S. Update on the diagnosis and treatment of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome: a review. JAMA Oncol 2021; 7: 1383-1391.

[3] Dispenzieri A. POEMS syndrome: 2021 update on diagnosis, risk-stratification, and management. Am J Hematol 2021; 96: 872-888.

[4] Keddie S and Lunn MP. POEMS syndrome. Curr Opin Neurol 2018; 31: 551-558.

[5] Brown R and Ginsberg L. POEMS syndrome: clinical update. J Neurol 2019; 266: 268-277.

[6] Nozza A, Terenghi F, Gallia F, Adami F, Briani C, Merlini G, Giordano L, Santoro A and Nobile-Orazio E. Lenalidomide and dexamethasone in patients with POEMS syndrome: results of a prospective, open-label trial. Br J Haematol 2017; 179: 748-755.

[7] Misawa S, Sato Y, Katayama K, Nagashima K, Aoyagi R, Sekiguchi Y, Sobue G, Koike H, Yabe I, Sasaki H, Watanabe O, Takashima H, Nishizawa M, Kawachi I, Kusunoki S, Mitsui Y, Kikuchi S, Nakashima I, Ikeda S, Kohara N, Kanda T, Kira J, Hanaoka H and Kuwabara S. Safety and efficacy of thalidomide in patients with POEMS syndrome: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2016; 15: 1129-1137.

[8] Ibrahim D, Froberg B, Wolf A and Rusyniak DE. Heavy metal poisoning: clinical presentations and pathophysiology. Clin Lab Med 2006; 26: 67-97.

[9] Wu ML, Deng JF, Lin KP and Tsai WJ. Lead, mercury, and arsenic poisoning due to topical use of traditional Chinese medicines. Am J Med 2013; 126: 451-454.

[10] Mo T, Sun S, Wang Y, Luo D, Peng B and Xia Y. Mercury poisoning caused by Chinese folk prescription (CFP): a case report and analysis of both CFP and quackery. Medicine (Baltimore) 2016; 95: e5162.

[11] Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR and Sadeghi M. Toxic mechanisms of five heavy metals: mercury, lead, chromium, cadmium, and arsenic. Front Pharmacol 2021; 12: 643972.

[12] Levin-Scherz JK, Patrick JD, Weber FH and Garabedian C Jr. Acute arsenic ingestion. Ann Emerg Med 1987; 16: 702-704.

[13] Gorby MS. Arsenic poisoning. West J Med 1988; 149: 308-315.

[14] Hall AH. Chronic arsenic poisoning. Toxicol Lett 2002; 128: 69-72.

[15] Shannon RL and Strayer DS. Arsenic-induced skin toxicity. Hum Toxicol 1989; 8: 99-104.

[16] Oh SJ. Electrophysiological profile in arsenic neuropathy. J Neurol Neurosurg Psychiatry 1991; 54: 1103-1105.

[17] Jackson R and Grainge JW. Arsenic and cancer. Can Med Assoc J 1975; 113: 396-401.

[18] Li L, Jiang B, Lai J, Dai WR, Li X, Liu WF, Yang ZX and Xie L. Change in peripheral nervous conduction velocity in patients with occupational chronic mercury poisoning and related influencing factors. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2017; 35: 598-602.

[19] Suichi T, Misawa S, Beppu M, Takahashi S, Sekiguchi Y, Shibuya K, Amino H, Tsuneyama A, Suzuki YI, Nakamura K, Sato Y and Kuwabara S. Prevalence, clinical profiles, and prognosis of POEMS syndrome in Japanese nationwide survey. Neurology 2019; 93: e975-e983.

[20] Nakanishi T, Sobue I, Toyokura Y, Nishitani H, Kuroiwa Y, Satoyoshi E, Tsubaki T, Igata A and Ozaki Y. The crow-fukase syndrome: a study of 102 cases in Japan. Neurology 1984; 34: 712-720.

[21] Dispenzieri A, Kyle RA, Lacy MQ, Rajkumar SV, Therneau TM, Larson DR, Greipp PR, Witzig TE, Basu R, Suarez GA, Fonseca R, Lust JA and Gertz MA. POEMS syndrome: definitions and long-term outcome. Blood 2003; 101: 2496-2506.

[22] Li J, Zhou DB, Huang Z, Jiao L, Duan MH, Zhang W, Zhao YQ and Shen T. Clinical characteristics and long-term outcome of patients with POEMS syndrome in China. Ann Hematol 2011; 90: 819-826.

[23] Dispenzieri A. POEMS syndrome: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol 2014; 89: 214-223.

[24] Abe D, Nakaseko C, Takeuchi M, Tanaka H, Ohwada C, Sakaida E, Takeda Y, Oda K, Ozawa S, Shimizu N, Masuda S, Cho R, Nishimura M, Misawa S, Kuwabara S and Saito Y. Restrictive usage of monoclonal immunoglobulin lambda light chain germline in POEMS syndrome. Blood 2008; 112: 836-839.

[25] Kanai K, Sawai S, Sogawa K, Mori M, Misawa S, Shibuya K, Isose S, Fujimaki Y, Noto Y, Sekiguchi Y, Nasu S, Nakaseko C, Takano S, Yoshitomi H, Miyazaki M, Nomura F and Kuwabara S. Markedly upregulated serum interleukin-12 as a novel biomarker in POEMS syndrome. Neurology 2012; 79: 575-582.

[26] Pulivarthi S and Gurram MK. An atypical presentation of POEMS syndrome with IgG kappa type M protein and normal VEGF level: case report and review of literature. J Cancer Res Ther 2018; 14: 679-681.

[27] Li Q, Xu F, Duan JF and Tang YF. Atypical polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes syndrome without polyneuropathy: a case report. Medicine (Baltimore) 2020; 99: e20812.

[28] Fonseca R, Bailey RJ, Ahmann GJ, Rajkumar SV, Hoyer JD, Lust JA, Kyle RA, Gertz MA, Greipp PR and Dewald GW. Genomic abnormalities in monoclonal gammopathy of undetermined significance. Blood 2002; 100: 1417-1424.

[29] Ye W, Wang C, Cai QQ, Cai H, Duan MH, Li H, Cao XX, Zhou DB and Li J. Renal impairment in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome: incidence, treatment and outcome. Nephrol Dial Transplant 2016; 31: 275-283.

[30] Nakamoto Y, Imai H, Yasuda T, Wakui H and Miura AB. A spectrum of clinicopathological features of nephropathy associated with POEMS syndrome. Nephrol Dial Transplant 1999; 14: 2370-2378.

[31] Roels H, Gennart JP, Lauwerys R, Buchet JP, Malchaire J and Bernard A. Surveillance of workers exposed to mercury vapour: validation of a previously proposed biological threshold limit value for mercury concentration in urine. Am J Ind Med 1985; 7: 45-71.

[32] Lai MW, Boyer EW, Kleinman ME, Rodig NM and Ewald MB. Acute arsenic poisoning in two siblings. Pediatrics 2005; 116: 249-257.

[33] Aymaz S, Gross O, Krakamp B, Ortmann M, Dienes HP and Weber M. Membranous nephropathy from exposure to mercury in the fluorescent-tube-recycling industry. Nephrol Dial Transplant 2001; 16: 2253-2255.