

Commentary

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Commentary on: Middle East Pain Syndrome is A Pollution-Induced New Disease Mimicking Rheumatoid Arthritis

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Middle East Pain Syndrome (MEPS) is a newly discovered disease, which may be one of the consequences of environmental pollution with heavy metals such as cadmium. It was named so, because all of the patients were from the Middle East, though it might affect people all over the world.

This syndrome comprises a chronic vitamin D3 deficiency or insufficiency, secondary hyperparathyroidism, and fibromyalgia.

Hyperparathyroidism was first linked to arthritis in (1963)¹, and then in (1983). Arthritis was found in 11% of hyperparathyroid (HPT) patients, with incidences of erosive arthritis². Other case studies²⁻⁶ had also described HPT presenting as arthritis. Meanwhile, HPT can coexist with inflammatory arthritis such as rheumatoid arthritis on rare occasions⁷.

In addition to clinical and biochemical characteristics, radiographic characteristics were useful in distinguishing RA and HPT. In contrast to the proximal interphalangeal joints (PIP) of rheumatoid arthritis, HPT can generate bone erosions that are shaggy throughout appearance and scattered in the radiocarpal, radioulnar, metacarpophalangeal, and distal interphalangeal joints⁸ (Table 1-3).

Table 1: Demographic data of MEPS study group

MEPS	No	%	ACPA	Age years	Female Sex		Duration years
					N	%	
Seropositive	72	18 %	0%	40±13	220	55%	1.27±0.82
Seronegative	328	82 %	0%	39±16	180	45%	1.17±0.90
Total	400	100 %	0%	40±15	400	50%	1.22±0.86

Table 2: Laboratory chemistry and PTH results of MEPS study group

	No	ESR mm	SUA mg/dl	Ca mg/dl	Ca++ mg/dl	D3 ng/ml	PTH pg/ml	P mg/dl
MEPS	400	40 ±14	6.4 ±1.3	8.6 ±1.4	1.11 ±0.11	15.58 ±6.66	96 ±12	4.8 ±1.2

ESR: erythrocyte sedimentation rate, SUA: serum uric acid, Ca: total calcium, Ca++: ionized calcium, D3: vitamin D3, PTH: parathyroid hormone, P: serum phosphorus

Table 3: Different Criteria Domains in MEPS study group

	NO	RN	Dur	CCP	RF	TTP	SSS	WPI
MEPS	400	0 %	1.22±0.86	0%	18%	15.2±2.3	9.62±2.11	15.32±3.34

RN: rheumatoid nodules, Dur: duration, CCP: anti-CCP, RF: rheumatoid factor, TTP: tender trigger points, SSS: symptom severity score, WPI: widespread pain index

Bone resorption and formation are both present in HPT. Bone resorption and sclerosis of many locations in the skeletal system may occur⁹. Subperiosteal resorption, brown tumors, bone cysts, and sclerosis were found on radiographs, along with osteoclastic resorption of bone, osteoblastic bone production, and fibrous replacement of marrow¹⁰ (Table 4).

Subchondral, subperiosteal, endosteal, intracortical, trabecular, subligamentous, and subtendinous bone resorption are all possible. The early and nearly pathognomonic symptom of HPT is subperiosteal bone resorption, which is characterized by marginal erosions with contiguous bone resorption and sclerosis¹⁰ (Figure 1, 2). HPT osteoporosis has a distinct tubal, cigar, or pyramidal look that differs from that of RA or other collagen disorders¹⁰ (Figure 1, 2).

Table 4: Different radiological findings in MEPS study group

Group	NO	Sr	Odp	Bt	Rj	Cs	ch	Ts	WA
MEPS	400	88 %	12	30%	30%	45%	20%	95%	35

Sr: Subperiosteal resorption, Odp: Osteolysis of distal phalanges, Bt; Brown tumours, Rj: Rigger jersey appearance of vertebral column, Cs :Calcaneal spurs, ch: chondrocalcinosis, Ts: Tuft spur-like excrescences. WA: wrist arthritis

What distinguishes MEPS from other diseases as hyperparathyroidism, psoriatic, or rheumatoid arthritis, is the presence of tuft spur-like excrescences mimicking that of spade phalanx sign of acromegaly¹¹, but without any other criteria of acromegaly. One literature reported this sign in an unexplained case report¹² (Figure 1-4).

Rheumatoid factor (RF) was present in 18% of our patients in low titers, with the absence of anti-cyclic citrullinated peptides antibodies (ACPA). As we know, rheumatoid factor (RF) is not exclusive to RA and can be present in many other conditions such as Epstein-Barr virus or Parvovirus infections, as well as in 5 to 10% of the normal population, especially elderly people^{13,14}. Although our patients were ACPA negative, it is important to note that positivity for ACPA is not diagnostic alone for RA without accomplishment of RA diagnostic criteria. ACPA are produced locally at areas of inflammation, not just in the synovium of RA patients, but also in non-RA conditions. As a result, ACPA positivity may be seen in a subset of patients with diseases other than RA¹⁵.

Of course, secondary hyperparathyroidism in our patients is caused by a series of chronic vitamin D3 shortage, and is not caused by renal issues, malignancies,



Figure 1



Figure 2

Figure 1, 2: Plain X ray hand PA view shows mild subperiosteal bone resorption affecting radial aspects of the proximal and middle phalanges of the 2nd and 3rd fingers, terminal tuft erosions (acro-osteolysis), as well as spur-like excrescences. Figure 1: Shows changes in the carpus closely resembling those of rheumatoid arthritis, radiocarpal and scapho-trapezoid joint arthritis.



Figure 3

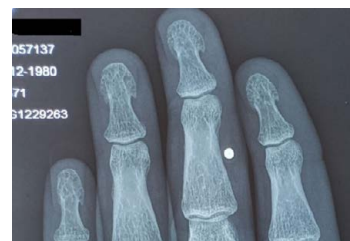


Figure 4

Figure 3, 4: Zoom of previous Plain X ray hands PA view shows tuft spur-like excrescences mimicking that of (spade phalanx sign) of acromegaly.

or other reasons. This chronic vitamin D3 shortage was ascribed to possible long-term exposure to the heavy metal cadmium, which is found in some mineral waters, carbonated beverages, fried foods, and tobacco smoke¹⁶.

Other possible causes of vitamin D3 shortage in the Middle East despite its plentiful sunshine, are limited sun exposure due to cultural practices, dress styles, limited time spent outdoors, and prolonged breast-feeding without vitamin D supplementation¹⁷.

As we know, vitamin D is produced in skin and some other tissues, and metabolized by the liver and kidney into 1,25 dihydroxy vitamin D3 (1,25 (OH)₂ D₃), the main circulating form of vitamin D. In these pathways, the steroidogenic enzyme cytochrome P450_{sc}, play key roles primarily in the kidney¹⁸⁻²¹.

Cadmium prefers to accumulate in the kidneys especially in S1 and S2 segments of the proximal tubules, which are responsible for converting 25(OH) D₂ to 1,25(OH)₂ D₃. Cadmium-metallothionein (CdMT) accumulation causes damage in the proximal convoluted tubules, and may contribute to CdMT-induced nephrotoxicity²². Cadmium was also discovered to block the production of the Cytochrome P450_{sc} gene, and therefore its steroidogenic activity²³.

Vitamin D3 deficiency as well as HPT have been linked to fibromyalgia syndrome^{24,25}.

Because of the continual removal of calcium from bone, hyperparathyroidism causes bone discomfort and painful joints in people with osteoporosis or osteopenia, as well as chondrocalcinosis and pseudogout. Hemorrhages within the bone can also cause bone discomfort. Calcium pyrophosphate deposition can cause joint discomfort, degenerative arthritis, joint laxity, and muscular weakening²⁶.

The exact incidence of this syndrome is not established yet, because it needs more cohort and multicenter studies. In our practice, more than 40% of previously diagnosed seronegative RA patients, who were not responding to treatment, were found to have MEPS. The diagnosis of this syndrome is not considered without the presence of both tuft spur-like excrescences and arthritis. Otherwise, it could be fibromyalgia or HPT.

This syndrome responds well to a fibromyalgia therapy regimen that includes antidepressants, muscle relaxants, and vitamin D3 supplementation of 5000-10000 iu/day, as well as antioxidants such as selenium, vitamins E, and C. We added sulphasalazine 1 gm/bid or Plaquenil 200 mg/bid to instances with arthritis, to which their inflamed joints responded dramatically. Treatment is continued as long as patient is complaining, with modifications according to the patient status, and it may last for 2 years or more. We

advised all patients to abstain from smoking or exposure to smoke; to change food habits to avoid cadmium polluted sources; to change their life styles as much as they can to expose to more sun light, and to practice gymnastics.

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