CASE REPORT

Environmental sensitivity as a trigger of erythema nodosum and perimenopausal symptoms

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SUMMARY

A 45-year-old woman presented to the University of Arizona Integrative Medicine Clinic for advice on managing recurrent erythema nodosum (EN), along with recent onset perimenopausal symptoms. Her painful EN flares had occurred two to six times per year over the past 14 years, yet had attenuated over the past 5 years until recently, and she presented with bilateral EN lesions on the shins. An environmental exposure history revealed that a new plastic-containing water pot had been introduced at her office just prior to her latest EN flare. She was told to eliminate environmental exposure to plastics, including this new coffee pot. She eliminated exposures to heated plastics, and replaced her coffee pot with a stainless steel one. Within weeks of removing these potential environmental triggers, her EN lesions cleared completely, and her menses normalised. An unintentional re-exposure to plastics 2 months later resulted in an EN recurrence within 2 hours.

BACKGROUND

Erythema nodosum (EN) has been associated with numerous autoimmune conditions, drugs and infectious agents. Typically, such occurrences are accompanied by constitutional symptoms such as fever, polyarthralgia and malaise. Between 17% and 72% of cases of EN are attributed to idiopathic aetiologies.[1–3] While infectious EN may resolve within weeks, idiopathic EN may last up to 6 months. No previously published reports in the literature have associated EN outbreaks with environmental triggers.

CASE PRESENTATION

We saw a 45-year-old woman in good health who presented to the University of Arizona Integrative Medicine Clinic with recent onset perimenopausal symptoms, along with a 14-year history of episodic flares of bilateral, lower extremity EN.

The EN flares were rated as mild–moderate, were self-limited and occurred two to six times per year. She describes them as painful bumps on her shins. She first experienced EN at 31 years of age during her first pregnancy, which ended with a miscarriage and spontaneous passage of the fetus. At the time, serology for valley fever was negative.

She experienced recurrences of the EN with her second and third pregnancies. These pregnancies were carried to full term and produced healthy babies. No aetiology was identified.

At age 35, the patient had a long episode of illness with myriad symptoms including back pain, mental fog and nausea. She describes that she was incapacitated with fatigue and needed much rest. No diagnosis was formally obtained, but her inflammatory markers were reportedly elevated. She was treated with a course of rofecoxib which helped dramatically, although briefly. This was followed by two short courses of oral corticosteroids. Eventually, she was diagnosed with pleurisy as a potential cause of her back pain. Over a 3-year period, she gradually regained her health.

Over the last 5–6 years, she reports that she has been in very good health, with one to two episodes of EN per year. When seen in our clinic, the patient had a persistent EN flare with two or three painful pretibial lesions for the past 6 months. She also recently began experiencing irregular menstrual cycles with cramping, heavy bleeding, hot flashes, mood irritability and disturbed sleep.

Her medical history was otherwise benign. Her family history was positive for uterine fibroids in her mother.

She takes no prescription medications, but takes cholecalciferol 1000 units daily, along with evening primrose oil, calcium and omega-3 fish oil 1000 mg.

She exercises 5 days per week with running and has a daily meditation practice.

INVESTIGATIONS

Screening laboratory tests, including hepatic and renal panels, as well as a complete blood cell count with differential, were within normal ranges. Tests of sedimentation rate, C reactive protein, antinuclear antigen (ANA) panel, thyroid function and celiac testing (tissue transglutaminase antibody) were unremarkable. Hormone levels (dehydroepiandrosterone, estradiol, progesterone and testosterone) were within expected values for a premenopausal woman. The only abnormal laboratory result was a slightly low 25-hydroxy vitamin D level (27 ng/mL). She had two small thyroid cysts on ultrasound, and a mammogram remarkable only for 'heterogeneously dense' breast tissue.

DIFFERENTIAL DIAGNOSIS

Consideration was given to diverse causes, including food sensitivities, vitamin D deficiency, uterine fibroids or an autoimmune disease.

Given this patient's age, it would be logical to suspect that her changes in menstrual symptoms were due to natural ageing, and to the hormonal

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fluctuations present during the perimenopause. The reappearance and persistence of EN that had previously been so closely tied to pregnancy and menses in the past could easily have been attributed solely to the onset of menopause.

Without an awareness and consideration of potential environmental contributors, this patient might have been told that her symptoms were related to normal ageing, and that she should either begin pharmacological treatment (eg, an selective serotonin reuptake inhibitor or hormonal replacement) or learn to live with the symptoms.

TREATMENT

While awaiting laboratory test results, a modified elimination diet was recommended (wheat, dairy, soy, citrus, corn and egg avoidance) along with instructions to maintain a symptom diary. In addition, given that all three pregnancies were associated with EN flares, it was hypothesised that oestrogenic or endocrine-disrupting properties of environmental chemicals may be a cause of the symptoms. An environmental handout with suggestions regarding avoidance of potential triggers (eg, bisphenol A (BPA) or phthalates) was provided.

After 12 days, the patient reported she had made a mental inventory of environmental exposures and discovered a potential cause. Just prior to her most recent flare, a new office worker was employed who brought an old water kettle that was partially made of plastic into the office. The patient noted she had been drinking coffee from it every afternoon. Based on this finding, the patient replaced the kettle with a 100% stainless steel unit, and replaced her plastic-containing drip coffee maker at home with a glass French press. She also changed her body lotion to one which did not contain methyl parabens. Finally, she stopped using plastic food storage or cooking vessels.

OUTCOME AND FOLLOW-UP

Within weeks of removing these potential environmental triggers, she observed that her menses normalised and her EN lesions cleared completely.

This finding alone would be provocative, however it was strengthened when a re-exposure led to an additional EN episode. Two months after eliminating plastic exposures, the patient microwaved a frozen dinner in a plastic bowl. Within 2 hours of eating the dinner, a characteristic EN lesion recurred on her lower extremity. This resolved within a day.

DISCUSSION

The association between environmental chemical exposure and endocrine abnormalities, including early menopause, has previously been suggested.[4] One presumptive trigger, BPA is a chemical used in the production of plastics and epoxy resin. It is a common component of polycarbonate water bottles and is used as liners in consumer canned goods.

Medically, BPA is a known endocrine disruptor that has been implicated in early puberty, infertility, breast cancer and abnormal menstrual periods. It has also been tied to obesity, prostate cancer, and neurodevelopmental problems in children.[5] Surveys of the amount of exogenous chemicals found in our bodies show that endocrine disruptors are increasingly common. A subset analysis of the 2003–2004 National Health and Nutrition Survey survey of adults in the US found BPA in over 90% of >2500 single urine samples examined.[6] With over 8 billion pounds of BPA produced annually, BPA is abundant in the environment. It is used in in food and drink containers (especially plastic containers and metal can liners), as well as in sunscreens and cosmetics. BPA is even found in cardboard and paper receipts.[7]

BPA was originally investigated as a potential synthetic pharmaceutical oestrogen in the 1930s, before diethylstilbestrol was shown to be more potent and began to be prescribed for pregnancy.[8] There is concern that the hormonal effects of BPA and similar chemicals can occur at even lower concentrations than had previously been established as safe; in addition, different physiological manifestations can present at lower doses than at higher doses. With the ubiquity of BPA and other hormone disrupters, it is important to realise the medical implications of these environmental exposures.

The WHO estimates that 25% of deaths worldwide may be attributable to environmental chemicals,[9] yet physicians learn very little about these exposures, or risks of illness, in their training. A 2014 survey of obstetricians revealed that only 1 in 15 reported receiving training in environmental health.[10] Fortunately, this deficit may soon be corrected.[11–14]

In summary, we evaluated a patient who developed EN and perimenopausal symptoms in response to an environmental trigger. Evaluation of environmental exposures and their endocrine-disrupting effects should be considered in patients presenting with unexpected symptoms including perimenopausal symptoms or idiopathic EN.

Learning points

- Erythema nodosum (EN) is frequently associated with autoimmune conditions, infections or drugs; however, up to 70% of the outbreaks are classified as idiopathic.
- Environmental causes have not typically been considered in the differential diagnosis of EN, but may be present in a substantial number of the so-called idiopathic cases.
- A careful environmental history, though commonly ignored, can reveal important sources of potentially harmful compounds encountered in the everyday life of a patient.
- Unexpected or unusual perimenopausal (or other hormonally-regulated) symptoms warrant evaluation of possible environmental triggers and a trial of 'exposure elimination' for several weeks or months.

Contributors Both authors made substantial contributions to the conception, design of the work, as well as the acquisition, analysis and interpretation of data for the work; drafted the work and revised it critically for important intellectual content. They both approve the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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