CASE REPORT

Psoriatic Arthritis

银屑病关节炎

Artritis psoriática

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ABSTRACT

Autoimmune diseases (ADs) are chronic, often debilitating and potentially life-threatening conditions that collectively affect up to 23.5 million Americans, and their incidence is rising.[1] They are heterogeneous in pathology but share common etiopathogenic factors such as intestinal hyperpermeability.[2] Although up to 100 ADs have been identified, there are likely more.[1] Genetics plays a clear role in the predisposition for the development and phenotype of AD, but various combinations of factors, such as toxins, endogenous hormone imbalances, microbes (including of GI origin), infections, stress and food antigens, are involved in disease expression.[2-5] Standard treatments include NSAIDs, steroids, anti-neoplastic agents and tumor necrosis factor-alpha antagonists. These tools have potentially devastating side effects and are often applied regardless of the diagnosis. Frequently, they are only modestly effective in relieving symptoms and limiting the advancing disease process. Direct healthcare costs of AD are estimated at around 100 billion dollars per year in the United States. By comparison, cancer care costs about 57 billion dollars per year.[1] The rising incidence of this debilitating and costly group of conditions dictates that safe, alternative approaches to treatment be considered now.

简介

自身免疫性疾病 (Autoimmune diseases, AD) 属于慢性疾病，此类疾病经常会使人变得虚弱并可能危及生命，患有此类疾病的美国人多达 2350 万，并且患病率正不断上升。[1] 它们在病理学上属于异质疾病，但是却具有相同的疾病发生基因因素，例如肠内渗透性过高。[2] 虽然已确定多达 100 种 AD，但数量可能更多。[1] 遗传在 AD 的发展和显型素质中起重要作用，但是疾病表达涉及不同的因素组合，例如毒素、内源性激素失衡、微生物（包括 GI 成因）、感染、压力和食物抗原。[2-5] 标准治疗包括 NSAID、类固醇、抗肿瘤药以及肿瘤坏死因子 α 阻滞剂。此类工具可能导致严重的副作用，使用时通常不考虑诊断结果。通常，它们仅对缓解症状并防止疾病进一步恶化起一定作用。在美国，AD 的直接健康护理成本大约为每年 1000 亿美元。比较起来，癌症护理成本约为每年 570 亿美元。[1] 衰弱病例的不断增加造成医疗成本剧增，因此，现在必须找到安全、可替代的治疗方法。

SINOPSIS

Las enfermedades autoinmunitarias (EA) son enfermedades crónicas, a menudo debilitantes y potencialmente mortales que, en su conjunto, afectan a 23,5 millones de estadounidenses, y su incidencia continúa en aumento.[1] Su patología es heterogénea, pero todas comparten factores etiopatogénicos comunes, como la hiperpermeabilidad intestinal.[2] Aunque se han identificado hasta 100 EA, posiblemente existan más.[1] La genética desempeña un papel claro en la predisposición a la aparición y el fenotipo de una EA; sin embargo, diversas combinaciones de factores, como las toxinas, los desequilibrios de las hormonas endógenas, los microorganismos (incluidos los de origen GI), las infecciones, el estrés y los antígenos alimentarios están implicados en la expresión de la enfermedad.[2-5] Los tratamientos habituales son los siguientes: AINE, esteroides, agentes antineoplásicos y antagonistas del factor de necrosis tumoral alfa. Estas herramientas tienen efectos secundarios potencialmente devastadores y, a menudo, se aplican con independencia del diagnóstico. Con frecuencia, solo tienen una eficacia moderada para aliviar los síntomas y limitar el avance del proceso patológico. Se calcula que los costes sanitarios directos de las EA ascienden a unos 100 000 millones de dólares al año en los Estados Unidos. En comparación, los costes sanitarios relacionados con el cáncer ascienden a aproximadamente 57 000 millones de dólares al año.[1] El incremento de la incidencia de este grupo de enfermedades debilitantes y costosas exige que se estudien planteamientos terapéuticos alternativos.

Table 1 56-Year-Old Male With Psoriatic Arthritis*

Additional Symptoms and Conditions	Psoriasis and psoriatic nails, constipation, esophageal reflux, aphthous stomatitis, blepharitis, migraines, and depression
Medications	Etodolac (Lodine), methotrexate, and adalimumab (Humira)
Tests Used	IgG food-specific antibodies, celiac panel with genes, inflammatory markers, and a multiprofile panel assessing nutrients, fatty acids, amino acids, organic acids, oxidative stress, and whole blood toxic metals. DNA-based stool analysis, complete blood count, and comprehensive metabolic panel with insulin and A1C
Imbalances Identified	Multiple IgG food sensitivities, intestinal hyperpermeability, gastrointestinal candidiasis, hypovitaminosis D, low red blood cell magnesium, elevated arachidonic acid, subclinical hypothyroidism, metabolic syndrome, suspected fatty liver
Treatments	Diet: 100% gluten and dairy free; avoid yeast and eggs; discontinue alcohol, caffeine, sugar; fluconazole; gastrointestinal anti-inflammatory medicinal food; probiotics; vitamin D; EPA/DHA; methyl donors (B_{12}, folic acid, B_6); amino acids (taurine, glycine, N-acetyl- cysteine, methionine); high-dose multivitamin and mineral without iron; daily meditation practice
Outcome	80% reduction in pain with improved mobility; stiffness and swelling resolved; discontinued NSAID and adalimumab (Humira®); reduced methotrexate; improved mood; resolved reflux and constipation; weight loss
Discussion/Significance	Using a systems medicine approach, including a comprehensive history, laboratory analysis and treatment, allowed the underlying imbalances of this case to be successfully identified and treated. A systems research model, able to capture and analyze complexity, would be well-suited to assess the efficacy of this type of multi-variable and individualized approach. If deemed effective on a larger scale, such an approach may be a logical solution for those suffering from complex, chronic diseases including AD.

*This case was modified with permission by Kara Fitzgerald, ND, and Mark Hyman, MD, and published by The Institute for Functional Medicine in its *Textbook of Functional Medicine*, 2010.

CASE HISTORY

At age 56, MP presented with a diagnosis of psoriatic arthritis that was progressively worsening despite aggressive medication therapy. He experienced severe pain, decreased range of motion, and swelling in his feet, ankles, knees, and hands. He walked with a limp. His left shoulder was also frequently painful. All symptoms became worse in the morning. He had been taking etodolac and methotrexate for the past 3 years, and adalimumab for the past 6 months. The onset of psoriatic arthritis occurred with the development of pain and redness in his right great toe, for which he was treated unsuccessfully with antibiotics. Shortly thereafter, he developed psoriasis behind his knees, on his feet, and behind his ears. He had psoriatic nails for most of his life.

Just prior to receiving the diagnosis of psoriatic arthritis, he had a left knee arthroscopy that was negative for degenerative disease but positive for synovitis. He also developed a hemorrhagic Baker's cyst, causing severe swelling and pain in his left foot and knee. MP also complained of esophageal reflux, a recent 15-pound weight gain, and intermittent depression.

MP's past medical history included migraine headaches and disc protrusion with sciatica at L5-S1. His mother, at age 82, was diagnosed with congestive heart failure, malnutrition, rheumatoid arthritis, depression, and schizophrenia. MP's father died at age 62; he had suffered from cancer, obesity, and alcoholism. His brothers were diagnosed with cancer, inflammatory arthritis, inflammatory bowel disease, alcoholism, and depression and his sisters with alcoholism, depression, and bipolar disorder. MP's son was diagnosed with schizophrenia and his daughter with ADHD. There was hypertension, diabetes, heart disease, and depression on both sides of the extended family.

In addition to etodolac, methotrexate, and adalimumab, MP took aspirin, omega-3 fatty acids, and a multivitamin and mineral. His past history included multiple courses of antibiotics.

MP led a stressful life with a highly demanding job. His schedule had little time for relaxation, although he reported meditating daily. MP was married with two children, including one who had been diagnosed with schizophrenia and lived at home.

MP's usual dietary intake included oatmeal with milk and sugar for breakfast; tuna with soup and cookies for lunch; fish or meat with vegetables and potato or pasta for dinner. He snacked on cookies and protein bars. He avoided chocolate and fatty foods. He ate out more than 5 times per week and craved sweets and caffeine, consuming 3 to 4 cups of coffee and one diet soda per day (357-464 mg caffeine). MP drank about 12 alcoholic beverages per week, including wine and the occasional scotch. He reported that his liver enzymes had been elevated, and he showed some concern about his drinking. Because of his schedule, he didn't exercise regularly, but he was interested in starting. He had a history of mold exposure and his teeth contained many mercury amalgams.

Table 2 IgG (total) Reactive Foods*

Almond (+2)	Chili Pepper (+2)	Lobster (+1)	Sesame (+1)
Amaranth (+1)	Clam (+2)	Milk, Cow's (+2)	Shrimp (+1)
Barley (+1)	Corn (+1)	Onion (+1)	Tomato (+1)
Bean, Kidney (+1)	Crab (+1)	Oyster (+2)	Wheat (+2)
Cantaloupe (+1)	Cranberry (+1)	Pineapple (+1)	Yeast, Baker's (+3)
Cashew Nut (+1)	Egg (+3)	Potato, White (+1)	Yeast, Brewer's (+4)
Cheese (+1)	Garlic (+1)	Scallops (+2)	

*Results range from 0 (no reaction) to +5 (severe reaction).

In his systems review, it was found that he was sensitive to loud noises, had dry eyes with crusty secretions, was intolerant of perfumes and auto exhaust, and had canker sores, esophageal reflux, and chronic constipation. He also had some difficulty with concentration and irritability. His blood pressure was 138/87, height 70.5", weight 204 lbs and body mass index was 28.85.

INITIAL LABORATORY RESULTS

Laboratory tests ordered and rationale:

1. IgG foods: Food reactions have been associated with psoriatic arthritis pathogenesis, and may contribute to inflammation. Many IgG reactions demonstrate intestinal hyperpermeability, also a factor in inflammatory arthritis. Removing offending foods, if present, will reduce systemic inflammation.
2. DQ genotype (celiac genes) and celiac panel: Celiac disease and psoriatic arthritis have been linked and share common inflammatory etiopathogenic features.
3. Inflammatory markers: Monitoring general inflammatory markers is standard practice for assessment of treatment efficacy.
4. Multiprofile panel: A comprehensive assessment including fatty acids, amino acids, organic acids, oxidative stress markers, and whole blood toxic metals. These tests assist in finding individual etiopathogenic factors that can affect treatment considerations. (Not all findings are discussed below. Panel results not grouped together)
5. Metabolic panel and lipids: General assessment of metabolic imbalances associated with inflammation
6. Thyroid panel: Subclinical hypothyroidism is frequently found in those with complex, chronic disease.
7. DNA microbial stool profile: Assessment of GI microbial status and GI function. GI imbalances are a common finding in inflammatory conditions.

Given MP's high number of amalgams, there was concern about mercury. According to the CDC, up to 75% of an individual's mercury exposure may be from amalgams.[7] MP's whole blood toxic metals were within normal limits, ruling out significant current toxic release from amalgams. A DMPS-challenged urine toxic element test was also ordered to assess body burden, but MP had not completed the test at the time of this publication.

Initial Assessment

- Psoriatic arthritis
- Psoriasis
- Psoriatic nails
- Blepharitis
- Aphthous stomatitis
- Gastroesophageal reflux disease
- Chronic constipation
- Migraine headaches
- Depression
- Intestinal hyperpermeability
- Gl
- Gluten sensitivity
- Multiple IgG food sensitivities
- Hypovitaminosis D
- Inflammation and oxidative stress
- Suspected fatty liver
- Metabolic syndrome
- Subclinical hypothyroidism
- GI yeast overgrowth
- Mercury toxicity (multiple amalgams)
- Family history of heart disease, hypertension, psychiatric disorders, diabetes, autoimmunity

Initial Plan

- Dietary changes: 100% gluten and dairy free; avoid yeast and eggs; discontinue alcohol, caffeine, sugar; eat whole, low glycemic-index foods, good fats, and proteins. Recommend prepared hypoallergenic meals.
- Anti-inflammatory medicinal food, 2 scoops QD
- 450 billion CF U probiotic, 1 packet BID
- Vitamin D3 5000 IU, 2 caps QD
- EPA/DHA 6:1, 1 cap BID
- Methyl donors (B_{12}, folic acid and B_6), 1 cap BID
- Amino acids (taurine, glycine, N-acetyl-cysteine, methionine), 3 caps BID
- High-dose multivitamin and mineral without iron, 4 tabs BID
- Fluconazole 100 mg, 1 tab QD x 30 days
- Continue daily meditation practice

Treatment plan rationale: Treatment for MP was focused on removing the antigenic foods and GI yeast, reducing inflammation, restoring GI mucosa, and providing needed nutrients. It was expected that thyroid and metabolic imbalances would normalize with these general interventions. Given his busy lifestyle, MP benefited from hypoallergenic, low glycemic index–prepared meals. Fluconazole was given for the Candida, followed by a mucosal-restoring medicinal food and high-dose probiotic.

Omega-3 fatty acids were given to support production of anti-inflammatory eicosanoids. Vitamin D (10,000 IU/day) was given to increase serum D levels to within 55 to 70 ng/mL, which is considered an optimal range in complex chronic disease. A supplement containing methyl donors was given to improve methylation and sulfuration activity based on the understanding that increased activity in these pathways may help with mood, metabolic imbalances, cardiovascular health and hepatic detoxification. The amino acid combination of taurine, glycine, N-acetyl-cysteine (NAC), and methionine was also prescribed to support hepatic methylation and sulfuration.[8-11] Taurine, glycine, and NAC are also known to have anxiolytic properties.[12-14] A high-dose multivitamin and mineral supplement was given for general micronutrient support, and to ensure adequate availability of cofactors and coenzymes. Metabolic polymorphisms can result in a lowered affinity of an enzyme for its coenzyme; thus, increased levels may be needed for optimal (or even adequate) functioning.[15,16] MP was encouraged to continue with his meditation practice, as meditation has been shown to improve well-being by reducing stress, inflammation and depression.[17-20]

Five-month Follow-up

MP arrived pain-free the day of the office visit, stating that he hadn't felt so good in years. He reported an 80% reduction in pain on average with improved mobility. He could climb stairs more quickly and was no longer limping. Morning pain and stiffness were gone. Previously, his hands were swollen and difficult to open. Now, the swelling was resolved and movement was normal. MP had not used any nonsteroidal anti-inflammatory or adalimumab for two months. He reduced his usage of methotrexate from 15 to 5 mg per week.

His reflux and migraines were gone. His mood had improved and he was less irritable.

He reported having a single, well-formed bowel movement daily. He was still under a great deal of stress, working 80 hours a week, but meditation continued to be helpful. He reported that he was still getting occasional canker sores.

He quit caffeine and reduced alcohol intake considerably. He started hypoallergenic, gluten-, yeast-, dairy-, and soy-free prepared meals, which were perfect for his busy lifestyle, enabling him to follow the dietary suggestions. He was taking his supplements regularly. He was losing weight, his clothes fit much better and he was satisfied with his dietary changes. Overall, he was pleased with his progress.

- Blood pressure: 118/73 LAS (5 months ago: 138/87)
- Pulse: 58 BPM
- Weight: 190 lbs (5 months ago: 204 lbs)

DISCUSSION

MP was taking a powerful combination of commonly prescribed medications for autoimmune conditions, including etodolac, methotrexate and adalimumab. Unfortunately, MP's symptoms continued to worsen. Laboratory analysis helped to reveal the etiology of MP's condition, enabling an effective treatment plan to be designed.

In Figure 1, ELISA testing for total IgG response to 90 different foods demonstrated a strong positive reaction to eggs and yeast, and mild positive reactions (+1 or +2) to 25 other foods, including gluten-containing wheat and barley. Food sensitivities generate significant inflammation and as such are both a cause and effect of intestinal hyperpermeability.[21-23]

Other factors contributing to MP's intestinal hyperpermeability included alcohol and NSAID use.[24,25] Intestinal hyperpermeability has been demonstrated to be a significant etiopathogenic mechanism in inflammatory arthritis and celiac disease.[2]

MP's genetic test for celiac disease demonstrated the presence of the DQ2 allele DQA1*0501 (Figure 1). Psoriatic arthritis is associated with celiac disease and subclinical gluten enteropathy.[26] HLA DQ is a heterodimer cell surface type protein found on antigen-presenting cells. HLADQ2 is encoded by the DQA1*0501 and the DQB1*0201 alleles. Approximately 90% of celiac

Celiac Disease Panel	Results	Reference Interval
Immunoglobulin A	438	82–453 mg/dL
Transglutaminase IgA	< 20	< 20 Units

Test	Results
DQ genotype	Allele Detected: HLA DQA1*0501

Figure 1 Food-specific IgG antibodies, celiac panel, and DQ Genotype. IgG food sensitivities demonstrated multiple reactions consistent with intestinal hyperpermeability. Celiac genes revealed a single allele that may be associated with increased risk of gluten intolerance.

patients express the DQ2 heterodimer serotype. Interestingly, more than 3% of celiac patients present with only half the DQ2 heterodimer, as did MP. In one study looking at 1008 European celiac patients, 57 encoded only half of the DQ2 heterodimer.[27] Because MP's test results demonstrated the presence of half the DQ2 heterodimer—specifically, the HLA DQA1*05 allele—celiac disease could not be ruled out. However, IgA tissue transglutaminase antibodies (tTG) were undetectable (Figure 1), which significantly reduced the likelihood of celiac disease.

Despite the equivocal celiac panel, a gluten-free trial was suggested because of the positive IgG reaction to wheat and barley and the presence of the DQ2 allele. It was also recommended that he eliminate dairy and those foods with reactivity of +3 and above and limit intake of the +2 foods.

Figure 2 showed reported levels of inflammatory markers, vitamin D and red blood cell magnesium. With the exception of a high-normal ferritin and elevated hs-CRP, none of the inflammatory markers were abnormal. Methotrexate and adalimumab attenuate markers of inflammation and may have been responsible for these negative findings.[28-30]

MP's vitamin D level of 21 ng/mL (Figure 2) may have contributed to the severity of his symptoms. The pathophysiology of psoriatic arthritis includes upregulation of Th1-driven inflammation. Vitamin D specifically regulates T-helper and dendritic cell function while inducing regulatory T-cells, causing a decrease in Th1 activity.[31,32] The optimal serum vitamin D range is now thought to be 40 to 70 ng/mL. It is suggested that individuals with chronic disease maintain levels between 55 and 70 ng/mL.[33] Hypovitaminosis D may have been a factor in MP's depression.[34] Suboptimal magnesium (Figure 2) is found in a large percentage of the population and is a common finding in those with chronic disease.[35]

In Figure 3, the omega-3 fatty acids (ALA, EPA and DHA) were all within normal limits, probably because MP was supplementing with them. However, the omega-6 fatty acid arachidonic acid (AA) was high normal, supporting the production of pro-inflammatory cytokines. The 2- and 4-series eicosanoids, produced from AA, stimulate the up regulation of TNF-alpha, a Th1 cytokine strongly implicated in psoriatic arthritis pathogenesis.[36] MP was taking the drug adalimumab, which binds TNF-alpha directly, blocking its ability to bind certain receptors.[37] Reducing AA availability through diet and nutrients could similarly assist in modulating the inflammatory effects of psoriatic arthritis by reducing AA-derived eicosanoids.

Figure 3 showed elevated saturated and monounsaturated fatty acids, which represent a pattern seen in metabolic syndrome with hypertriglyceridemia, where insulin stimulates the liver enzyme fatty acid synthase to produce saturated fatty acids. Insulin also stimulates delta-9 desaturase which converts saturated to monounsaturated fatty acids, primarily palmitoleic, vaccenic and oleic.[38] Lipid peroxidation was also high, indicating increased oxidative damage to the lipid-rich cellular membranes.[39]

Inflammatory Markers		Results	Reference Interval
Iron		80	50–150 µg/dL
Transferrin		246	201–336 mg/dL
TIBC		308	255–450 mg/dL
Iron saturation		26	20–50%
Ferritin	HN	322	23–336 ng/mL
ESR Westergren		7	0–20 mm/hr
CRP high sensitivity	HN	2.9 mg/L	Relative cardiovascular risk: Low < 1.0; Average 1.0–3.0; High 3.1–10.0
Rheumatoid factor		< 20	< 30 IU/mL
ANA screen		Negative	Negative

Test		Results	Reference Interval
Vitamin D 25 OH	L	21 ng/mL	< 20 ng/mL: Insufficiency 20–40 ng/mL: Hypovitaminosis D 40–100 ng/mL: Sufficiency > 100 ng/mL: Toxicity

Figure 2 Inflammatory markers, vitamin D, and RBC magnesium. Significant findings revealed a high-normal ferritin level. Medications may have been dampening the other inflammatory markers. He also had hypovitaminosis D and low magnesium. Deficiencies of both may contribute to inflammation.

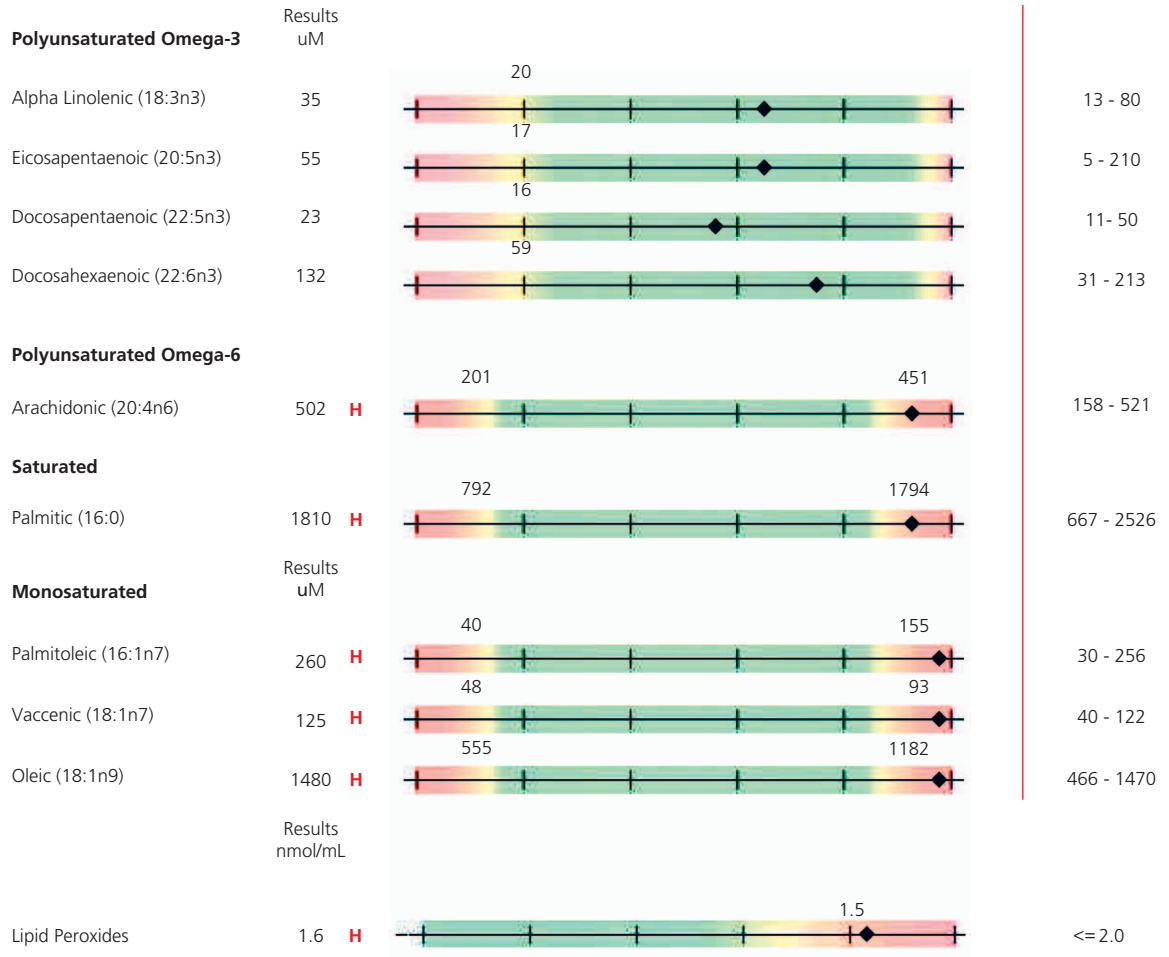

Figure 3 Plasma fatty acids and lipid peroxides. Omega-3 fatty acids were at normal levels, probably as a result of MP's supplementation. However, the pro-inflammatory fatty acid arachidonic acid (AA) was high-normal and much more abundant than the anti-inflammatory eicosapentaenoic acid (EPA). The plasma saturated and monounsaturated fatty acids demonstrated elevations consistent with hypertriglyceridemia and dysinsulinemia. Serum lipid peroxide elevation indicated increased oxidative damage to lipid membranes.

The metabolic assessment shown in Figure 4 demonstrated insulin resistance. It has been suggested that insulin stimulates the production of AA,[40] and AA elevation has been associated with insulin resistance.[41,42] These findings suggested a possible mechanistic link between psoriatic arthritis and metabolic syndrome through the common pathway of eicosanoid-driven inflammation. An elevated AA/EPA ratio has been shown to positively correlate with depression.[43] MP had more than 7 times the amount of AA relative to EPA in his plasma, despite supplementation with omega-3 fatty acids.

MP's thyroid panel was within normal limits, including antibodies (Figure 5). Optimal TSH is now considered to be 2.5, but may be as low as 1.18 mIU/L.[6] Free T3 and free T4 were low normal. These results suggested that the thyroid should be monitored, particularly given the association of hypothyroidism with rheumatologic conditions. Nutrients involved with thyroid function, including red blood cell zinc, whole blood selenium and plasma tyrosine, were within normal limits.

As was suspected, DNA stool analysis demonstrated a significant quantity of Candida species in the gastrointestinal tract (Figure 6). Candida species in particular have been found in significant amounts relative to controls in the saliva, skin, and stool of psoriatic patients.[44]

As discussed above in the treatment rationale, a straightforward approach involving removing yeast and antigentic foods was used to address the imbalances found, reducing inflammation, restoring GI mucosa and providing the needed nutrients. It was expected that thyroid and metabolic imbalances would be normalized with these general interventions.

CONCLUSION

Autoimmune diseases are debilitating conditions that affect millions of individuals.[1] Current standard-of-care therapies come with high risk profiles and may not slow the progression of the disease significantly.[45] Despite the extensive categorization of autoimmune diseases into diagnoses such as lupus, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, multiple

Metabolic Panel	Results	Reference Interval
Glucose	H 106	70–99 mg/dL
Insulin	HN 21	6–27 uIU/mL
Glycohemoglobin A1C	5.5	4.4–6.8%
ALT	H 44	0–40 IU/L
Lipids	**Results**	**Reference Interval**
Cholesterol, Total	H 218	< 200 mg/dL
Triglycerides	H 431	< 150 mg/dL
Cholesterol, HDL	H 43	40–59 mg/dL
Cholesterol, LDL	*Not analyzed due to interference of elevated triglycerides*	< 130 mg/dL

Figure 4 Metabolic panel and lipids. MP's metabolic panel demonstrated findings consistent with metabolic syndrome, including a mild elevation of ALT, which may indicate early hepatosteatosis.

Thyroid Panel	Results	Reference Limits
TSH	HN 2.39	0.28–3.89 mIU/L
T4, Free	LN 0.58	0.58–1.64 ng/dL
T3, Free	LN 2.9	2.5–3.9 pg/mL
Thyroglobulin Ab	< 20	< 40 IU/mL
Thyroid Peroxidase Ab	< 20	< 35 IU/mL

Figure 5 Thyroid panel. The thyroid panel demonstrated subclinical hypothyroidism. Current thinking on thyroid stimulating hormone (TSH) is that an optimal level may be 2.5mIU/L or less.[6]

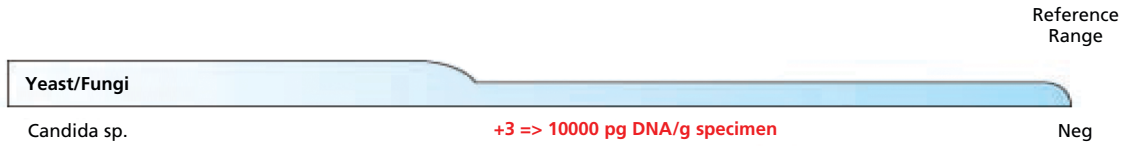

Figure 6 Microbial stool analysis using DNA identification. An elevated amount of Candida DNA was identified in the stool.

sclerosis, nephritis, and scleroderma, the treatments are based on pathology, not etiology. The conventional approach to autoimmune disease seeks to answer the question of *what* disease the patient has, not *why* the patient has the disease, suggesting only small variations in treatment.

Systems-based, or functional, medicine considers the diagnosis, of course, but also seeks to answer the question *why*. The etiology of a disease may vary among people with the same diagnosis or pathology. Conversely, the etiology may be the same in patients with very different pathologies—for example, mercury toxicity is found in both multiple sclerosis and Crohn's disease. Approaches to treatment, therefore, will vary according to the particular upstream causes and downstream effects present in each patient. Treating only the downstream effects (such as nutrient deficiencies or food sensitivities due to malabsorption and intestinal hyperpermeability) without treating the upstream causes (such as gluten sensitivity, gastrointestinal yeast, or mercury toxicity) will often result in treatment failure.

Focusing on the patient's individual etiology of autoimmune disease provides a personalized framework for diagnosis and treatment. Five primary etiologic factors have been identified that give rise to nearly all disease (including autoimmune disease) through their effects on gene expression: toxins, allergens, infections (or microbial imbalances), poor diet, and stress.

MP, a highly successful, educated physician had access to the latest medications and technologies to address his psoriatic arthritis. Unfortunately, however, his condition continued to deteriorate despite aggressive interventions. He was in constant pain, with limited mobility and use of his hands. Using a systems approach with MP including laboratory analysis and thorough history allowed the variables involved in the etiopathogenesis of his illness to be successfully identified and addressed. His pain was alleviated, his movement restored and his quality of life immeasurably improved. Associated complaints such as reflux, constipation, migraines and depression were all resolved in the process, as they all shared pathogenic mechanisms

with PA. He was able to reduce the dosage or eliminate all of his medications. As MP became versed in understanding the environmental role in his condition, he was able to identify and avoid his disease triggers, allowing him to take charge of his health.

Employing a systems research model to explore multivariable treatment approaches, such as the one used with MP, will allow for a non-biased assessment of the efficacy of such approaches. Following this model of care, if demonstrated to be broadly efficacious, may be beneficial for addressing the rising incidence of complex, chronic disease.

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