CLINICAL CARE CONUNDRUM

# Caught in the Web: e-Diagnosis

**The approach to clinical conundrums by an expert clinician is revealed through presentation of an actual patient's case in an approach typical of morning report. Similar to patient care, sequential pieces of information are provided to the clinician who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring the patient and the discussant.**

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**A 52-year-old woman** presented with a 3-month history of progressive bilateral leg edema and dyspnea while climbing a flight of stairs or while walking up a steep slope. She also complained of a tingling sensation in both hands and fingers, which started about 2 months prior to the onset of edema. She did not describe sensory problems in the lower extremities and did not have any other neurological complaints. She denied fever, cough, chest pain, palpitations, orthopnea, paroxysmal nocturnal dyspnea, and dark stools. She had no history of hypertension, diabetes, dyslipidemia, or asthma and had never been hospitalized. She did not smoke or consume alcohol and used no medications, including over-the-counter drugs or dietary supplements. The patient was born in Japan and had not traveled outside the country since her birth. She was a homemaker and had worked occasionally as a manual laborer in sugar cane agriculture. A review of systems revealed no history of polydipsia, polyuria, or cold or heat intolerance but did identify new hair growth, especially on the extremities.

This middle-aged woman shows progressive changes in her general health status that are characterized by edema and dyspnea on effort. The differential diagnosis of edema includes a broad spectrum of illnesses, such as cardiac, lung, renal, endocrine, and hepatic diseases. Because of the life-threatening potential, my first concern is cardiac disease, although the patient is not experiencing typical symptoms of ischemic heart disease or congestive failure. Bilateral and distal distribution of neuropathic symptoms is likely due to diseases of peripheral nerves rather than those of the central nervous system. Her complaint of a bilateral tingling sensation in the hands may suggest carpal tunnel syndrome as a result of her long-term agricultural work. Other possible causes include radiculopathy of the cervical spine or polyneuropathy. Clues in the physical examination may help narrow the differential diagnosis to a cardiac, hepatic, or endocrine disorder.

**The patient appeared ill**. Her weight had increased from 48 to 61 kg since she was last weighed 6 months previously. Her blood pressure was 140/78 mm Hg, her heart rate was 72 beats/minute with a regular rhythm, her respiratory rate was 18/minute, and her temperature was 37.5°C. The jugular venous pressure was elevated at 10 cm above the sternal angle. A grade III/VI systolic ejection murmur was evident at the second interspace along the left sternal border. The second heart sound was fixed and split. There were decreased breath sounds and complete dullness to percussion over both lower lung fields. Shifting dullness was noted on abdominal examination. There was pitting edema from the feet to the thighs, with slow pit-recovery time in both legs, and she exhibited generalized hirsutism on the face, body, and extremities. There was no lymphadenopathy. On neurological examination, her mental status was normal. The cranial nerves were normal, as was coordination. There was mild generalized distal-dominant motor weakness with generalized hyporeflexia. Sensory testing demonstrated glove-and-stocking type loss of sensation to pinpricks as well as dysesthesia in all extremities. Phalen and Tinel tests were negative.

The elevated venous pressure and pitting edema with slow recovery suggest high venous pressure edema rather than hypoproteinemic edema. Complete bilateral dullness of the chest and shifting dullness of the abdomen indicate the presence of bilateral pleural effusion and ascites. Edema from high venous pressure is usually caused by right, left, or biventricular cardiac failure. A fixed splitting of the second heart sound suggests an atrial septal defect, which is a rare cause of progressive right heart failure in adults. I recommend checking the patient's thyroid function to investigate the possibility of hypothyroidism, which is a common illness among middle-aged women and could contribute to her edema as well as hirsutism. The neurological findings suggest a generalized polyneuropathy. The unusual combination of high venous pressure edema and polyneuropathy may indicate a rare multisystem disorder such as amyloidosis. Alternatively, the patient might have developed multiple diseases during the same time period. For instance, diabetic polyneuropathy is the most common cause of polyneuropathy among the middle-aged. Finally, the differential diagnosis of hirsutism includes ovarian, adrenal, or pituitary sources of hyperandrogenism in addition to hypothyroidism. I would first evaluate for diabetes, thyroid disease, and cardiac disease and would like to see the results of laboratory tests for thyrotropin and plasma glucose as well as chest radiography and electrocardiography.

**The white-cell count** was 5400/mm$^3$ with a normal differential. Hemoglobin was 10.7 g/dL with normal red-cell indices, and the

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platelet count was 276,000/mm$^3$. The erythrocyte sedimentation rate was 29 mm/hour. Other laboratory tests revealed the following values: total protein, 6.2 g/dL; albumin, 3.3 g/dL; blood urea nitrogen, 12 mg/dL; creatinine, 0.7 mg/dL; aspartate aminotransferase, 6 U/L; alanine aminotransferase, 2 U/L; lactate dehydrogenase, 96 U/L; alkaline phosphatase, 115 U/L; creatine phosphokinase, 60 U/L; total bilirubin, 0.9 mg/dL; glucose, 96 mg/dL; hemoglobin A1c, 4.6%; total cholesterol, 111 mg/dL; and thyrotropin, 6.32 mIU/mL (normal range, 0.50-5.00 mIU/mL). Serum free thyroxine, triiodothyronine, and urine testosterone were normal. Serum dehydroepiandrosterone sulfate was mildly elevated for her age (864 ng/mL: normal range, 180-750 ng/mL). Serological studies for human immunodeficiency virus, human T-lymphotrophic virus type 1, and syphilis were negative. Urinalysis was weakly positive for protein but negative for casts and occult blood. The stool was negative for occult blood.

**A chest radiograph** showed bilateral pleural effusions. Computed tomography demonstrated bilateral pleural effusions, ascites, mild hepatomegaly, and small, multiple, mediastinal lymph nodes. Her electrocardiogram was normal. A transesophageal echocardiogram with agitated saline contrast demonstrated normal ventricular systolic and diastolic function and no atrial septal defect. The inferior vena cava did not collapse with inspiration, and there was no evidence of infiltrative cardiomyopathy.

These laboratory results rule out diabetes as the cause of the polyneuropathy. The subclinical hypothyroidism would not explain profound edema and hirsutism. A serum albumin level of 3.3 g/dL confirms high venous pressure edema rather than hypoproteinemic edema. Normochromic, normocytic anemia and a mildly elevated sedimentation rate point to a chronic illness or inflammatory state. The mediastinal lymphadenopathy may reflect congestion as a result of the high venous pressure or reflect a systemic disease involving lymph nodes. Normal ventricular function with high venous pressure is suggestive of heart failure from diastolic dysfunction, although the patient does not have risk factors for diastolic dysfunction, such as hypertension, and has no other echocardiographic features of diastolic impairment. The combination of hyperandrogenism and neuropathy points to a systemic process, such as a paraneoplastic syndrome. I would next investigate the source of the excess androgens.

**Because serum dehydroepiandrosterone sulfate** was mildly elevated, I-131 aldosterol scintigraphy was performed, and it was negative. Electromyography showed a pattern of generalized sensorimotor polyneuropathy.

At this point, it appears that cardiac, endocrine, hepatic, and renal diseases have been largely ruled out as a cause of her symptoms. Reframing and unifying the important clinical problems for this patient may be useful in resolving this diagnostic puzzle. They include (1) systemic high venous pressure edema; (2) generalized sensorimotor polyneuropathy; (3) hirsutism; (4) normocytic, normochromic anemia; (5) an elevated erythrocyte sedimentation rate; (6) mediastinal lymphadenopathy; and (7) subclinical hypothyroidism. At this point, I cannot unify these pieces of information into a single diagnosis. I would search the medical literature, focusing on these terms.

**A general internist consultant** performed MEDLINE and Google Scholar searches using the key words ''edema,'' ''polyneuropathy,'' and ''hirsutism.'' This search suggested the diagnosis of Crow-Fukase syndrome, also known as POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome. Subsequent evaluations were performed. First, serum protein electrophoresis revealed the presence of monoclonal proteins, although hypergammaglobulinemia was not present. Second, a bone marrow examination demonstrated increased abnormal plasma cell proliferation (7%), although a radiographic skeletal survey found no lesions suggestive of plasmacytoma. Third, cerebrospinal fluid analysis showed normal cell counts but increased protein concentration (202 mg/dL). Fourth, a blood sample referred to an outside laboratory demonstrated elevated levels of vascular endothelial growth factor (3902 pg/mL: normal range, 150-500 pg/mL). On the basis of these findings, the diagnosis of POEMS syndrome was made. After oral prednisolone (40 mg/day) was initiated, the systemic edema improved gradually, and she did well during the 2-year follow-up period.

## Commentary

POEMS syndrome, also known as Crow-Fukase syndrome, is a rare multisystem disorder first described by Crow in 1956.[1,2] It is characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, as indicated by the acronym. The diagnosis of POEMS syndrome is difficult as this syndrome is rare and requires high clinical suspicion. According to a nationwide cross-sectional survey in Japan, the prevalence of POEMS syndrome is very low (about 3 patients per 1,000,000 persons),[3] and its prevalence in Western countries is considered even lower than that in Japan. The average age at onset is around 45 to 50 years old, and men are twice as likely to have this syndrome as women.[4–6] Table 1 shows the diagnostic criteria of POEMS syndrome, based on research by Dispenzieri and others at the Mayo Clinic, and Table 2 presents the relative frequency of these clinical features.[6,7] The initial symptomatology generally includes polyneuropathy, skin changes, and generalized edema, which are nonspecific symptoms, as are other well-recognized associated conditions such as clubbing, weight loss, thrombocytosis, polycythemia, and hyperhidrosis. Thus, it is important to consider this syndrome when one is facing an undiagnosed illness involving multiple organ systems and to distinguish it from other conditions such as multiple myeloma, amyloidosis, and monoclonal gammopathy of undetermined significance. Vascular endothelial growth factor is thought to be involved in the edema of POEMS syndrome, as massive release from aggregated platelets increases vascular permeability and venous pressure.[7–10]

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**TABLE 1. Criteria for the Diagnosis of POEMS Syndrome**

| | |
|---|---|
| Major criteria | Polyneuropathy |
| | Monoclonal plasma cell-proliferative disorder |
| Minor criteria | Sclerotic bone lesions |
| | Castleman disease |
| | Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) |
| | Edema (peripheral edema, pleural effusion, or ascites) |
| | Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, or pancreatic) |
| | Skin changes (hyperpigmentation, hirsutism, plethora, hemangiomata, and white nails) |
| | Papilledema |

NOTE: Two major criteria and at least one minor criterion are required for diagnosis. This table is based on the work of Dispenzieri.[7]

**Abbreviation:** POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.

**TABLE 2. Relative Frequency of Clinical Features in Patients with POEMS Syndrome (n = 99)**

| Characteristic | % |
|---|---|
| Peripheral neuropathy | 100 |
| Monoclonal plasma cell dyscrasia | 100 |
| Sclerotic bone lesions | 97 |
| Endocrinopathy | 71 |
| Skin changes | 68 |
| Organomegaly | 46 |
| Extravascular volume overload | 39 |
| Papilledema | 29 |
| Castleman disease | 11 |

NOTE: This table is based on the work of Dispenzieri.[7]

**Abbreviation:** POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.

Data regarding treatment and survival are largely observational. Overall mean survival from diagnosis in the 2003 Dispenzieri cohort was 13.7 years, with death often due to infection or cardiorespiratory failure.[6] When a solitary plasmacytoma or osteosclerotic myeloma is present, radiation to the lesion can often lead to clinical remission. Other treatment options include alkylating agents and/or high-dose chemotherapy with peripheral stem-cell transplantation, corticosteroids, and supportive care.[7]

Clinicians frequently use the internet to aid in the clinical decision process. In a survey of the Royal New Zealand College of General Practitioners,[11] half reported that they used the Internet to search for clinical information. Two well-known resources are MEDLINE, which contains over 11 million references dating back to the 1960s, and internet search engines such as Google (and a more recent product, Google Scholar, which attempts to sort search results by including factors such as the author, the publication in which the article appears, and how often the article has been cited).

MEDLINE searches a well-defined set of journals and uses the Medical Subject Headings (MeSH) vocabulary, which consists of sets of descriptive terms organized in a hierarchical structure to allow searching with various levels of specificity. For instance, entering the term "heart attack" will map to the MeSH term "myocardial infarction" and will also include more specific terms such as "myocardial stunning" and "cardiogenic shock."

Google, in comparison, explores resources beyond journals without any clear boundary to its scope, and its advanced search functions can be occasionally unreliable. For instance, search results are occasionally marred by outdated citation information and may include materials that are not truly scholarly. However, search engines can search through the actual text of manuscripts and access the "gray literature," which includes open-source material that is usually original but not widely distributed or often easily available, such as technical reports and dissertations. A direct study comparing the results of searches in PubMed (one of the MEDLINE search engines) and Google Scholar is difficult, but the critical characteristics of each can be compared and contrasted (Table 3).

Internet searches may also suggest diagnoses from a compilation of clinical features, such as in this case. To be successful, such a search must complement the cognitive process; a search engine cannot completely replace clinical judgment. Clinicians must be able to identify salient clinical features and generate high-yield search terms and then exercise skill in sifting through the citations to arrive at the appropriate diagnosis. A recent study found that Google searches revealed the correct diagnosis in 58% of the case records of the *New England Journal of Medicine*,[12] although each search query resulted in many results, which then had to be manually reviewed for appropriateness within the case's context.

Like a traditional diagnostic test, a search can be described by sensitivity, specificity, and the number of articles needed to read.[13] For example, in a study comparing the performance of search strategies to identify clinical practice guidelines in Google Scholar and SUMSearch (another freely accessible search engine), using the term "guideline" yielded the highest sensitivity, and using the term "practice guideline" generated the highest specificity and the lowest number of articles needed to read (Table 4).[14]

Although there are several other popular hosts of web-based search engines, a more robust decision-support program may help physicians more efficiently consider relevant diagnoses. One program, named Isabel, has been developed through the indexing of a database of more than 11,000 diseases according to word patterns in journal articles associated with each disease, and it is updated as new and relevant articles emerge. One recent study demonstrated that the correct diagnosis was made in 48 of 50 cases (96%) with specific, key findings as search terms but in only 37 of the same 50 cases (74%) if the entire case history was simply pasted in, again emphasizing the importance of specific search terms.[15]

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**TABLE 3. Strengths and Weakness of Google Scholar and PubMed**

| Google Scholar | PubMed |
|---|---|
| 1. Database selection is clumped under subject areas, and it cannot be searched with unique identifiers: Con | 1. It allows one to choose a database at the outset and can search with a unique identifier (PubMed identifier): Pro |
| 2. Results cannot be filtered (ie, it does not allow multiple article selection): Con | 2. The single citation matcher allows retrieval of articles with pieces of information: Pro |
| 3. A search for related articles or similar pages is not available: Con | 3. It allows article selection by checkbox to reduce the number of articles relevant to the search query and to append the filter to search box: Pro |
| 4. It allows one to search by "without" words to exclude unwanted and confusing retrieved data: Pro | 4. It provides unique identifier (PubMed identifier) for each retrieved article for easy communicability: Pro |
| 5. It allows one to search a single journal/publication of interest: Pro | 5. Search are limited to journals only; it does not include the grey area of literature: Con |
| 6. Initial search results are those articles that are most cited by journals that themselves are the most cited: Pro | 6. It lists search results in chronological order and not by relevance: Con |

**TABLE 4. Retrieval Performance of Search Strategies Using SUMSearch and Google Scholar**

| Search Strategy | Sensitivity (%) | Specificity (%) | NNR |
|---|---|---|---|
| SUMSearch | | | |
| Guideline* | 81.51 (74.53–88.49) | 74.29 (72.64–75.94) | 8.18 (6.90–10.05) |
| Recommendation* | 60.50 (51.72–69.28) | 76.28 (74.67–77.89) | 9.93 (8.14–12.72) |
| Practice guideline* | 40.34 (31.52–49.16) | 89.45 (88.29–90.61) | 6.96 (5.52–9.43) |
| Google Scholar | | | |
| Guideline/s | 31.93 (23.56–40.30) | 78.05 (76.50–79.60) | 16.67 (12.76–24.04) |
| Recommendation/s | 8.40 (3.42–13.38) | 92.11 (91.09–93.13) | 22.42 (13.97–56.82) |
| Practice guideline/s | 11.76 (5.98–17.54) | 95.72 (94.96–96.48) | 9.29 (6.21–18.38) |

NOTE: The 95% confidence intervals are shown in parentheses. This table is reprinted with permission from *BMS Medical Research Methodology.*[14] Copyright 2007, BioMed Central, Ltd.

**Abbreviation:** NNR, number needed to read.

*Truncation.

POEMS syndrome is a rare entity occasionally seen in middle-aged individuals and marked by a multitude of nonspecific findings, particularly polyneuropathy and plasma cell dyscrasia. In this case, the "diagnostic test" was an internet search based on the most prominent clinical symptoms. Such a strategy can provide a powerful addition to traditional literature and MEDLINE resources. However, the efficiency of this process is heavily dependent on the quality of the search strategy and, therefore, the cognitive faculties of the treating physician to avoid the predictable shortcoming of low specificity. "Garbage in, garbage out" still applies whether the computer in question is the human mind or the desktop PC.

## Teaching Points

1. POEMS syndrome, also known as Crow-Fukase syndrome, is a rare multisystem disorder characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.
2. Internet-based searches, including Google and MEDLINE, are being used more frequently because they are widely available, quick, and freely accessed.
3. Internet searches appear most useful as adjuncts to PubMed and clinical reasoning in identifying case reports when a well-constructed collection of symptoms and signs is used for searches.

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