nisone (10 to 20 mg/day). Patients in whom disease is not suppressed or patients in whom prednisone can not be tapered to lower doses after 1 month are given a combination of agents including MTX, parenteral gold, AUR, and HCQ. As disease is controlled, the most dangerous drugs are withdrawn in the hope of achieving maintenance control with the less toxic medications, such as HCQ or AUR. At the present time, 54 patients have been entered into this paradigm, and those with disease duration of less than 2 years have generally fared very well. Unfortunately, reduction to monotherapy alone has not been possible.

We have proposed the "graduated-step" paradigm. In this model, immediately after diagnosis is established, patients are numerically staged as having mild, moderate, or severe disease. Staging is based on the presence of prognostic factors and the level of disease activity. Those with mild disease receive HCQ and nonsteroidal anti-inflammatory drugs. Patients with moderate disease receive those drugs and may also be given a second disease-modifying agent, such as AUR, SSZ, or MTX. These patients may also be given low doses of prednisone. Patients with severe disease may be given up to three disease-modifying agents, including the three previous agents and DPN, parenteral gold, or AZA, at their initial visit. Disease control is maintained by applying a disease activity index at subsequent visits designed to control acute-phase reactants and limit the number of swollen tender joints to four or less. At this time, 16 patients have been entered into the paradigm and analysis is underway.

AN ESTIMATE OF THE EFFECT OF THE GRADUATED-STEP PARADIGM

Because the graduated-step paradigm is based on the style of treatment for RA in the Department of Rheumatic and Immunologic Disease at The Cleveland Clinic Foundation over the past 10 years, an estimate of the effectiveness of the paradigm was possible. We retrospectively analyzed the medical records of 34 consecutive RA patients seen in the department. We then compared their long-term outcome with existing series in the literature that show declining grip strength and functional capacity over time. The Westergren sedimentation rate was maintained below 30 mm/hour for most of our patients, and the joint count hovered around five during the period of treatment. Rather than falling, the mean grip strength of our patients improved and nearly doubled from the initial visit to the final visit, with a mean observation period of 8.3 years. Grip-strength improvement, as in other studies, was accompanied by improvement in functional class.

Although these retrospective data are not conclusive, they suggest that there is at least a subset of patients with RA who tolerate aggressive combination therapy and whose outcome is considerably better than has been previously reported.

CONCLUSION

It is unlikely that one therapeutic strategy or a single treatment modality will prove best for all patients with RA. A variety of therapeutic approaches is necessary. These approaches should emphasize early control of the biologic activity of the disease, which should result in improved function. These attempts at treatment should be performed as part of prospective, long-term, carefully documented trials, designed so that future analysis can determine which regimens are most effective and least toxic.

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CUSHING'S SYNDROME: EASY TO SEE, TRICKY TO DIAGNOSE

PATIENTS WITH CUSHING'S syndrome are usually easy to recognize. The round plethoric facies, supraclavicular and infrascapular fat pads, thinning of the skin, and truncal weight distribution are typical. Cushing's syndrome also is associated with proximal weakness, abnormal menses in women, impotence in men, and osteoporosis. The challenge is to determine whether the syndrome has a pituitary or nonpituitary cause.

Most patients with proven cortisol excess have Cushing's *disease*—an excess of pituitary-driven adrenocorticotropic hormone (ACTH) and cortisol. The others have adrenal disease or an ectopic (non-pituitary) ACTH-secreting neoplasm.

Surgical therapy is effective for most patients with pituitary Cushing's disease and for those with a single adrenal adenoma, although the initial cure rate for pituitary disease can be as low as 70% in the biggest and best surgical series. When cured, however, these patients can undergo profound improvements in appearance and behavior in a few months. The prognosis is not good for patients with adrenal cancer, since these tumors are often not resectable.

CLASSIFYING THE SYNDROME

The first diagnostic step is chemical confirmation of cortisol overproduction. The 24-hour urine free cortisol test has replaced measurement of 17-hydroxysteroids as the gold standard. Some still use the overnight dexamethasone suppression test, although this has less sensitivity.

If the 24-hour urine free cortisol test is positive, ACTH measurements can help classify what type of disease is present. Patients with adrenal disease usually have very low ACTH levels; patients with pituitary Cushing's disease have ACTH levels that range from normal to about twice the upper limit of normal levels; those with ectopic ACTH secretion have levels that are usually more than twice normal.

Imaging helps to confirm and localize the diagnosis by identifying the adrenal gland that needs to be removed, but the chemical diagnosis should be reasonably firm before progressing to imaging techniques. If biochemical testing clearly indicates an adrenal source, with very low ACTH levels, computed tomography (CT) may demonstrate one adrenal tumor, two large adrenals (macroadenomatous hyperplasia), or adrenals that look perfectly normal (Carney's complex, with nerve cell tumors and atrial myxomas as well as micronodular hyperplasia). But the same observations can occur in a patient who has pituitary disease. Many patients who in fact had pituitary Cushing's disease have had one adrenal gland removed because of such misleading radiologic findings. If the likely biochemical diagnosis is pituitary Cushing's disease, with normal to high ACTH levels, CT or magnetic resonance imaging (MRI) of the pituitary gland may be helpful, although the presumed tumor will be observed in only about half of patients.

The likelihood of false-negative and false-positive results must be considered when working up a patient with Cushing's syndrome. Because both cortisol and ACTH are stress hormones, patients with acute illness may appear chemically to have Cushing's disease. Gross obesity, alcohol abuse, depression, and the use of phenytoin and phenobarbital can cause false-positive urine free cortisol, ACTH, or dexamethasone test results.

About 5% to 10% of patients with Cushing's syndrome have intermittent or periodic secretion and will have negative results if tested during a nadir. As a general rule, if the index of suspicion is high for Cushing's syndrome because of symptoms, but chemical tests are negative, the patient should be tested again.

INFERIOR PETROSAL SINUS SAMPLING

The technique of inferior petrosal sinus (IPS) sampling was developed to resolve the diagnostic confusion of ectopic ACTH secretion originating from a non-pituitary tumor. The clinical, biochemical, and imaging features of pituitary Cushing's disease and ectopic ACTH secretion may be identical, or the picture may be equivocal. For example, a patient may have ACTH levels that favor a diagnosis of pituitary Cushing's syndrome, but dexamethasone testing shows no suppression and MRI shows no visible tumor. IPS sampling permits measurement of plasma ACTH in the petrosal sinuses and a peripheral vein both before and after administration of corticotropin-releasing hormone. When the gradient (IPS to peripheral) ACTH level is >3.0, the patient likely has pituitary disease.

The question of whether all patients with Cushing's syndrome should have IPS sampling is controversial. The procedure is invasive and, therefore, not risk-free. In a National Institutes of Health (NIH) series of 278 patients, IPS sampling identified only 9.3% of patients with occult ectopic ACTH syndrome, so its cost-effectiveness is questionable. At this point, we advise using it in selected patients. Based on NIH data, good candidates are those whose urine free cortisol levels fail to fall to ≤10% of baseline on the second day of a high-dose decadron test.

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SKIN LESIONS: WHEN TO SUSPECT SYSTEMIC CAUSES

The dermatologic manifestations of systemic disease cover a spectrum that includes autoimmune, neoplastic, and infectious disease. The following are some tips to increase awareness and suspicion of a few of these lesions.

PARANEOPLASTIC PEMPHIGUS

Paraneoplastic pemphigus, a distinct autoimmune disorder associated with neoplasms, was first described only 2 years ago. It produces skin lesions resembling erythema multiforme, lichen planus, or pemphigus vulgaris. Underlying malignancies include lymphoproliferative disorders and bronchogenic carcinoma. To date, eight cases have been reported in the literature, with four additional cases at the Cleveland Clinic (in press). The fact that four cases have occurred at one institution suggests that the disorder is more common than the literature indicates. It has been underrecognized because it was not known how to characterize the syndrome, which often has the appearance of erythema multiforme but is associated with cancer. If a cancer patient has erosive stomatitis, conjunctivitis, polymorphous erythema multiforme, or an eruption resembling bullous lichen planus, paraneoplastic pemphigus should be suspected. The diagnosis can be confirmed with indirect immunofluorescent testing on rat bladder transitional epithelium. The rat bladder test is easily performed, is inexpensive, and has a specificity of 98.9%. Treatment, in addition to managing the underlying tumor, involves immunosuppressive therapy with steroids or azathioprine.

METASTASIS

If a skin lesion proves to be a metastasis, suspect that the primary tumor originates from an organ under the site of the lesion and that the primary cancer is relatively common. In women, the most likely source of metastatic skin lesions is breast cancer. The chest and the abdomen are the most common sites of metastatic skin lesions.

HYPERSENSITIVITY

Erythema nodosum (eg, nodules on the lower legs, possibly tender) is an inadequate diagnosis. Erythema nodosum is really a hypersensitivity response to something else. The possible causes are many, and identification may require an aggressive search. Streptococcal infection is the most common cause, but also consider sarcoidosis, oral contraceptives, sulfonamides, barbiturates, fungal infections, or inflammatory bowel disease. Apart from addressing the underlying cause, treatment with a nonsteroidal anti-inflammatory drug or a steroid may be helpful.

VIRAL INFECTION

Consider herpes simplex virus (HSV) infection when a patient presents with symmetrical erythema multiforme, even when HSV is not clinically evident. In many cases of recurrent disease, testing by polymerase chain reaction will reveal HSV-specific DNA in the lesions. Steroids are of little therapeutic value, but acyclovir may be beneficial.

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