A 56-year-old woman with symptoms of carpal tunnel syndrome for 6 months presented to a referral clinic with nodular lesions on her right forearm and hand that had appeared 4 months before consultation. The lesions were associated with an increase in numbness and tingling in her right hand. She reported no weight loss, fever, chills, headaches, rashes, myalgias, or arthralgias. She did, however, describe intermittent night sweats.

The differential diagnosis of chronic nodular lesions is broad and includes infectious, inflammatory, and malignant causes. Common infectious causes include fungal and mycobacterial infections and nocardiosis. The history taking should include an assessment for potential exposures. For example, gardeners are at risk for sporotrichosis and nocardiosis, whereas tropical-fish owners who clean the aquarium may become infected with *Mycobacterium marinum*. Certain infections, such as leishmaniasis, myiasis, and visceral larva migrans, are associated with travel to particular geographic areas. Inflammatory causes of nodules include lupus erythematosus profundus and cutaneous polyarteritis.

During the previous 3 months, the patient had several appointments with an orthopedic surgeon for carpal tunnel syndrome. The surgeon performed an incision and drainage on one of the forearm lesions, and serosanguineous fluid was noted. No cultures were sent. Over the next 2 weeks, new lesions formed on the dorsum of her hand and on the palmar side at the base of the middle finger. A carpal-tunnel–release procedure was then performed on the right side; biopsy specimens of the lesions on her hand and forearm were obtained during the procedure. Pathological assessment of these biopsy specimens revealed granulomas with central necrosis and predominant neutrophilic infiltration. Gram’s stain and special stains were negative for bacteria, mycobacteria, and fungi. Cultures for all these organisms remained negative. The numbness and tingling in her arm persisted despite the release procedure, and new cutaneous lesions continued to develop. Eight weeks after the carpal-tunnel release, the patient was referred to an academic medical center.

The finding of suppurative granulomas is helpful in narrowing the differential diagnosis. Fungal and mycobacterial infections are the most common cause. Negative cultures and special stains raise the possibility of cutaneous tuberculosis; papulonecrotic tuberculids may have very few organisms. A chest radiograph and tuberculin skin test should be performed. Polymerase-chain-reaction assays for fungal, mycobacterial, and bacterial DNA on tissue (fresh-frozen or paraffin-embedded) may also be useful but are not widely available. Some cutaneous inflammatory conditions (e.g., drug-induced vasculitis, systemic lupus erythematosus, Sjögren’s syndrome, rheumatoid arthritis, scleroderma, or dermatomyositis) and lymphoma may also result
in granuloma formation. I am very interested in the patient’s exposure and occupational history.

The patient’s medical history was also notable for temporomandibular joint syndrome, anxiety, allergic rhinitis, and a long-standing heart murmur. She had annual tuberculin skin tests at her job at a medical clinic; after 13 years of negative tests, her most recent test 3 weeks earlier was positive, with 11 mm of induration; a chest radiograph was negative. Isoniazid was prescribed for latent tuberculosis. Her other medications included pyridoxine, alprazolam, escitalopram, conjugated estrogen and progesterin, and folic acid. The patient lived in the midwestern United States. She did not smoke and drank alcohol occasionally. She had no pets. She worked in a medical-records department but had no exposure to patients, and she was also a professional hairdresser. Her only recent travel was to Florida a year before her symptoms appeared, where she spent time on a beach collecting shells. She recalled injuring her thumb on a thorn on a separate occasion approximately 4 months before the nodular lesions appeared, and had pain and erythema that persisted for 4 weeks but then completely resolved without treatment.

The recent tuberculin-skin-test conversion, combined with the finding of granulomas, is suggestive of a cutaneous mycobacterial infection. Infection with atypical mycobacteria, as could have occurred with the patient’s thorn injury, could also cause tuberculin-skin-test conversion. An interferon-γ-release assay (IGRA) should be performed, because this assay has less cross-reactivity with atypical mycobacteria, and a negative result would be helpful in narrowing the differential diagnosis. In any case, a thorough search for an underlying focus of tuberculosis (e.g., a careful history taking and physical examination, complete blood count, chest radiograph, and urinalysis) is mandatory. To prevent the emergence of drug resistance, the isoniazid should be discontinued until active tuberculosis can be ruled out. The thorn injury might also be a source of infection with nocardia or fungi such as sporothrix.

On physical examination, the patient did not appear to be in distress and was alert and oriented. The temperature was 37°C, and lungs were clear on auscultation bilaterally. Cardiovascular examination revealed distinct heart sounds, regular rhythm, and a grade 2/6 systolic murmur radiating to the axilla. The abdomen was soft and nontender. The volar aspect of her right arm had a 6-cm surgical incision, with a violaceous area surrounding it. There was induration but no warmth or tenderness. The dorsal aspect of the arm was swollen from the hand to midway up the forearm. There were also multiple small, nodular lesions scattered on the dorsal surface of the hand, wrist, and forearm (Fig. 1). These lesions were nontender, and no discharge could be expressed. On the palm, there was scarring from the carpal-tunnel repair, along the thenar eminence. There was a firm, papulonodular lesion at the base of the right middle finger, which was erythematous and nontender. The patient held her right hand in a flexed position, and both active and passive movement of the right hand and wrist was painful. Examination of her left hand and other extremities showed no abnormalities.

I am concerned that the swelling may indicate infectious tenosynovitis, which may be caused by bacteria (e.g., *Neisseria gonorrhoeae* or *Staphylococcus aureus*), endemic fungi, or mycobacteria. The most likely diagnoses in this case remain a mycobacterial infection (tuberculosis or an atypical mycobacterial infection), an endemic fungal infection, and nocardiosis. An accurate diagnosis is critical for successful treatment, and it may be necessary to perform a repeat biopsy of one of the nodular lesions, with special stains and cultures and histopathological analysis of the biopsy specimen, as well as a polymerase-chain-reaction assay, if available.

The white-cell count was 4600 per cubic millimeter, with 55% neutrophils, 43% lymphocytes, and 2% monocytes. The hematocrit was 36%, and the platelet count 170,000 per cubic millimeter. Liver-function tests were normal. The creatinine level was 0.7 mg per deciliter (61.9 µmol per liter). The results of an electrolyte panel, including the calcium level, and urinalysis were normal. The erythrocyte sedimentation rate was 10 mm per hour, and the C-reactive protein level was 1 mg per deciliter. A chest radiograph was normal.

The results of the laboratory tests do not help differentiate among the infections previously discussed. Low levels of inflammatory markers and a normal white-cell count are typical findings in patients with localized chronic lesions of this type.
A repeat biopsy was performed on one of the skin lesions. Pathological analysis of the biopsy specimen revealed fibrosis and a patchy, mixed inflammatory infiltrate. Stains for bacteria, fungi, and acid-fast bacilli were negative; cultures were performed.

The pathological findings have not clearly revealed a cancer, and the patient does not have any other findings suggestive of an inflammatory disease. Given the tuberculin-skin-test conversion, I remain concerned that she has cutaneous tuberculosis, since the yield on culture and acid-fast bacilli staining may be low. Pending mycobacterial culture results, if there is clinical worsening, I would recommend collection of additional biopsy specimens from one or more of the nodules to help establish the diagnosis.

Because of worsening pain and increased limitation in wrist function, magnetic resonance imaging (MRI) of the patient’s right arm was performed. This showed extensive tenosynovitis in all the tendons of the forearm and a soft-tissue collection around the forearm (Fig. 2). The patient underwent explorative surgery, and several large-volume specimens from the soft-tissue collection were obtained for staining and additional cultures.

The MRI scan suggests extensive disease. In retrospect, it is likely that the cause of her carpal-tunnel symptoms was encasement of nerves by the infectious process.

Staining for acid-fast bacilli was positive (Fig. 3). A QuantiFERON–TB Gold (QFT) test (Cellestis) was negative, and isoniazid was discontinued.

Given the negative QFT test, M. tuberculosis is unlikely, and I agree with discontinuation of the isoniazid. A number of nontuberculous mycobacterial species, many of which have specific temperature and growth requirements, may cause skin and soft-tissue infections.

A culture for acid-fast bacilli was positive for M. marinum after 4 weeks. Treatment with clarithromycin and ethambutol was started. At a follow-up visit 3 months later, the lesions showed improvement. By the time the patient had completed antimycobacterial therapy, 9 months after the start of treatment, the nodules and all symptoms had resolved.

**Commentary**

M. marinum, a well-described cause of cutaneous infections, can lead to a variety of clinical presentations such as nodules, ulcers, tenosynovitis, or nodular lymphangitis. This water-borne organism is found both in naturally occurring bodies of water and in still or stagnant water, such as swimming pools and fish tanks, leading to the names “swimming pool granuloma” and “fish tank granuloma.” Infection usually occurs after direct inoculation through broken skin on exposure to fresh water or saltwater or after injuries from fish spines or oyster shells.

The incubation period of M. marinum is typically between 2 and 4 weeks, although incubation periods of more than 30 days have been reported. Pointed questions regarding skin injuries associated with water, fish, or shellfish may identify exposures that could otherwise be overlooked. The patient’s reported exposure was more remote than the recognized incubation periods, and it is likely that another exposure occurred that she did not recall.

The primary lesions of M. marinum are commonly described as superficial papules, nodules, plaques, ulcers, abscesses, or pustules occurring at the site of the injury. These superficial lesions are emblematic of M. marinum infections, because
the pathogen typically does not invade beyond the superficial, cooler regions of the skin; it thrives at temperatures between 30 and 33°C rather than at the body’s core temperature of 37°C. In a large common-source outbreak of M. marinum infections that involved 290 patients, no cases of deep soft-tissue infections were reported. However, there have been several reports of extension of infection into deep tissue, leading to tenosynovitis, arthritis, bursitis, or osteomyelitis, and substantial associated morbidity, including risks of joint immobility and the need for amputation.

The risks of untreated infection underscore the importance of timely diagnosis. Yet the nonspecific and often indolent presentation of M. marinum infection can make the diagnosis elusive. A detailed investigation of exposure history and culture or histopathological analysis of tissue are critical.

The positive tuberculin skin test provided an important clue in the present case. The tuberculin skin test may be positive in patients with prior vaccination with M. bovis bacille Calmette–Guérin (BCG) or exposure to environmental mycobacteria that share some of the antigens that are present in the tuberculin skin test. If M. tuberculosis exposure is unlikely, as it was in this low-risk patient, a positive test should prompt careful consideration of other causes.

IGRAs such as the QFT test and the enzyme-linked immunospot assay use enzyme-linked immunosorbence to measure antigen-specific production of interferon by circulating T cells in whole blood. In a meta-analysis of 38 studies, IGRAs had a sensitivity of 78% (95% confidence interval, 73 to 82) for latent tuberculosis infection, which is similar to the reported sensitivity of the tuberculin skin test. The specificity was 97.0%, which is greater than that of the tuberculin skin test in patients with a history of BCG vaccination. Neither test distinguishes between active tuberculosis and latent infection. Apart from the increased specificity, the main advantage of the IGRAs is that they require only a single patient visit. The Centers for Disease Control and Prevention has recommended that use of an IGRA be considered in any situation in which a tuberculin skin test is used.

The target antigens used in IGRAs are two proteins present in M. tuberculosis, early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These proteins are also present...
in some other mycobacteria, including *M. kansasii* and *M. marinum*, but the diagnostic usefulness of the IGRAs has not been validated for these conditions, and they are not recommended for these diagnoses. A recent study showed that 7 of 12 patients with *M. marinum* infection (58%) had a positive IGRA.14

This case also underscores the need to doggedly pursue the diagnostic standard — in this case, confirmation by culture, especially since empirical therapy can be misguided. *M. marinum* is typically resistant to isoniazid, and this agent was discontinued in favor of combination therapy with clarithromycin and ethambutol, two first-line drugs associated with excellent outcomes.4 Multiple biopsies were performed in this patient before surgically acquired samples finally yielded positive results. This is not unusual, since the number of organisms present is usually small. Smears for acid-fast bacilli are negative in up to 95% of tissue-biopsy specimens.15

Under appropriate conditions, mycobacterial culture is positive in approximately 80% of cases of infection. *M. marinum*, however, grows optimally at a temperature between 30 and 33°C. Unless the laboratory automatically processes skin and soft-tissue specimens at these lower temperatures for nontuberculous mycobacteria, failure to indicate the possibility of *M. marinum* on the initial request form frequently results in false negative results from tissue cultured at 37°C. Cultures must be held for at least 6 weeks before one can conclude that the results are negative, since *M. marinum*, like many other mycobacteria, is a slow-growing organism.4

Despite the substantial delay in proper identification of the infection, our patient did well after surgical débridement. After several months of treatment with first-line agents for *M. marinum*, her lesions — which ended up being more than just skin deep — fortunately resolved.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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**REFERENCES**


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