

Table 1. Incidence of the Primary End Point in Two Subgroups of Patients.*

Subgroup	Clopidogrel % of patients	Placebo % of patients	Hazard Ratio (95% CI)	P Value
Prior use of antiplatelet agents				
No	6.7	7.1	0.94 (0.83–1.07)	0.34
Yes	10.0	12.8	0.78 (0.51–1.18)	0.23
Aspirin dose				
<100 mg	6.5	6.9	0.94 (0.79–1.13)	0.50
100 mg	6.2	8.4	0.73 (0.59–0.90)	0.003
>100 mg	8.4	6.8	1.25 (0.98–1.60)	0.07

* The hazard ratio is for the comparison of the clopidogrel group with the placebo group. CI denotes confidence interval.

taking COX-2 inhibitors at the time of enrollment, there was no significant excess of myocardial infarction or effect on the primary end point with clopidogrel and aspirin, as compared with placebo and aspirin.

A question about the effect of the aspirin dose is raised by Kamalesh. Although there were no significant differences in the efficacy or safety end points between the group given placebo and aspirin and the group given clopidogrel and aspirin, the latter treatment showed less effi-

cacy and a trend toward a greater risk of bleeding with doses of aspirin exceeding 100 mg. We are in the process of preparing in-depth reports on these interesting issues that pertain to the subgroups and secondary analyses of the CHARISMA trial.

Eric J. Topol, M.D.

Case Western Reserve University
Cleveland, OH 44106-4955
eric.topol@case.edu

for the CHARISMA Investigators

Medical Mystery: Arthritis — The Answer

TO THE EDITOR: The medical mystery in the June 1 issue¹ involved a 51-year-old woman with a 15-year history of rheumatoid arthritis, who presented with swelling and a loss of function of the right shoulder. Microscopy of the synovial fluid drawn from this shoulder showed geometric plates with notched corners, pathognomonic of monohydrate cholesterol crystals (Fig. 1A). Analysis of the synovial fluid revealed a leukocyte count of 2100 per cubic millimeter, a total cholesterol level of 7.8 g per liter, a low-density lipoprotein cholesterol level of 6.1 g per liter, a high-density lipoprotein cholesterol level of 1.7 g per liter, and a triglyceride level of 0.83 g per liter. The plasma lipid profile was normal.

Cholesterol crystals are found only sporadically in the synovial fluid of patients with rheumatoid arthritis. Such crystals may appear in two morphologic forms: large, flat, rectangular plates that are negatively birefringent (doubly refract-

ing) with notched corners, ranging from 8 to 100 μm long and consisting of monohydrate cholesterol, or rod-shaped, helical birefringent crystals, ranging from 2 to 20 μm long and consisting of anhydrate cholesterol. Since these large cholesterol plates are difficult to clear, they are thought to play a role in the perpetuation of the arthritis.

Tim L. Jansen, M.D., Ph.D.

Anneke Spoorenberg, M.D., Ph.D.

Medisch Centrum Leeuwarden
8934 AD Leeuwarden, the Netherlands

Editor's note: We received 658 responses to this medical mystery from 59 countries. Fifty-nine percent of the responses were from physicians in practice, 21 percent from physicians in training, 13 percent from medical students, and 7 percent from other readers. As with past medical mysteries, many of the responses reflected a team effort

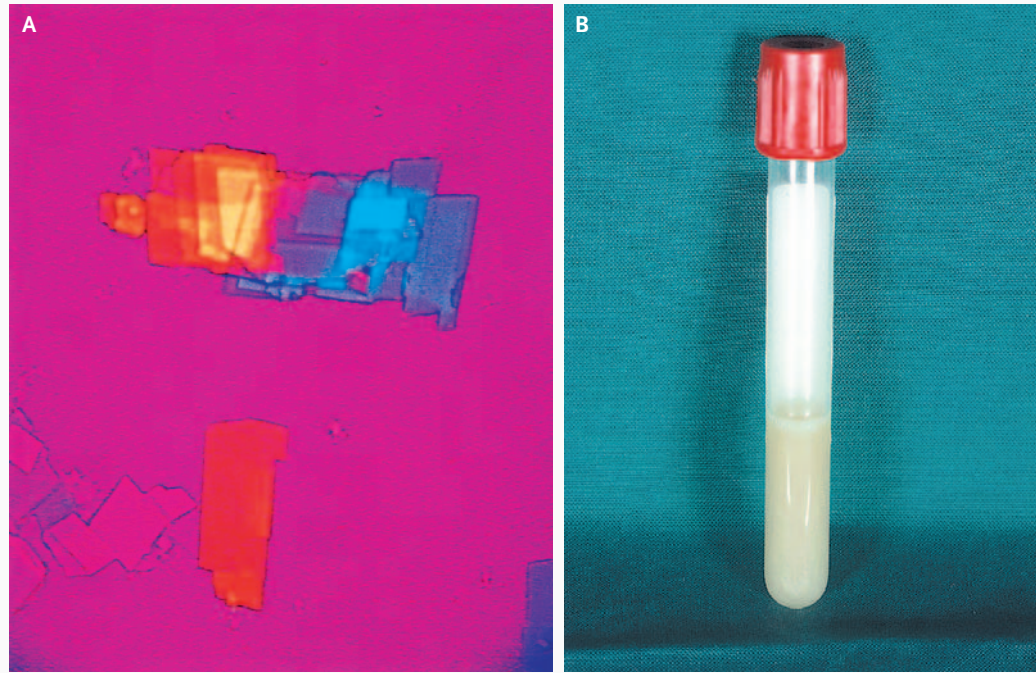


Figure 1. Cholesterol Crystals in Synovial Fluid.

In Panel A, monohydrate cholesterol crystals are identified on the basis of their geometric plates with notched corners. Panel B clearly shows the milky appearance of the patient's synovial fluid.

— such as members of a training program submitting a group response after discussing the case in a teaching conference.

Twenty-seven percent of the respondents correctly identified cholesterol crystals in the synovial fluid. Forty-nine percent suggested the presence of other crystalline diseases, including gout (urate crystals) and pseudogout (calcium pyrophosphate crystals). Nine percent suggested an infectious arthritis, such as that due to *Mycobacterium tuberculosis*, as the cause. The remaining 15 percent of

respondents suggested a variety of conditions, including amyloidosis, multiple myeloma, sarcoidosis, gold deposition from intraarticular injections, and a malignant effusion, to explain the findings.

Important clues to the correct diagnosis include the finding of variably birefringent, platelike crystals with notched corners under polarizing microscopy (Fig. 1A) and milky synovial fluid on gross analysis (Fig. 1B).

1. Jansen TL, Spoorenberg A. A medical mystery — arthritis. *N Engl J Med* 2006;354:2375.

Case 13-2006: A Man with a Bone Mass and Lesions in the Liver

TO THE EDITOR: In the Case Records presented in the April 27 issue,¹ which involved a patient with liver lesions and a bone mass in the right ulna, Hasserjian states that hepatocellular carcinoma “does not typically give rise to bony metastasis.” In fact, bone metastases occur with regularity in hepatocellular carcinoma. Specifically, in a sub-

group of 23 patients with metastatic hepatocellular carcinoma who received investigational thalidomide, bone lesions were present in 5 (22 percent) and were the third most common site of extrahepatic metastasis after lung and retroperitoneal lymph nodes.² My colleagues and I noted bone metastases in 19 of 57 patients (33 percent) who