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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 1-2014: A 32-Year-Old Man with Loss of Vision and a Rash

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PRESENTATION OF CASE

Dr. Janae K. Heath (Medicine): A 32-year-old man was admitted to this hospital because of loss of vision.

The patient was in his usual health until 3 weeks before admission, when painless conjunctival injection developed in the left eye, associated with dryness. He self-administered ophthalmic tetrahydrozoline solution, and the condition resolved. Approximately 1 week before admission, the symptoms recurred and progressively worsened. Discharge with crusting was present in both eyes in the mornings. Three days before admission, he noted loss of vision on awakening, with light perception in the left eye and blurred vision in the right eye; vision in the right eye reportedly improved slightly after the administration of ophthalmic tetrahydrozoline solution. Discharge from the eyes and crusting on the eyelashes persisted. On the morning of admission, a relative visited the patient at his home and took him to the emergency department at another hospital. On examination, the vital signs were normal. Ophthalmic abnormalities were reportedly noted. Laboratory results are shown in Table 1. A metal eye protector was placed over the left eye and normal saline was administered intravenously. He was transferred by ambulance to this hospital, for coordination of ophthalmic care with Massachusetts Eye and Ear Infirmary, which is affiliated with this hospital.

The patient reported that he had no ocular pain, pruritus, or grittiness and therefore had not sought evaluation earlier; reportedly it had been 1 week since he had looked in the mirror. He reported a 1-week history of pain in the right hip joint with radiation to the knee, a 3-week history of an acneiform rash on his face, and a 4-week history of rash on his lower legs. He reported no fevers, chills, night sweats, weight loss, oral ulcers, direct eye inoculation, or injury. He had hypertension and a history of alcohol and illicit inhalational drug use. He took no other medications and had no known allergies. He smoked cigarettes until the onset of this illness, when he also stopped alcohol intake; he reported no illicit drug use for 3 months. He lived alone and was unemployed. He reported that his father had "spine fusion disease" and that an aunt had had "transient blindness."

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On examination, the patient appeared older than his stated age. He was alert, oriented, pale, and thin, with temporal wasting. The vital signs and oxygen saturation were normal. The height was 181 cm, the weight 63.5 kg, and the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) 19.4.

Ophthalmologic examination revealed conjunctival injection in both eyes (2+ ciliary flush on the right, and diffuse 3+ injection on the left), with purulent crusting and discharge on the lashes, which was worse on the left eye (Fig. 1). Punctate epithelial erosions (also known as superficial punctate keratitis) were seen diffusely on the right cornea (worse inferiorly). On the nasal side of the left cornea, there was a perforated descemetocele (corneal thinning down to the innermost layer of Descemet's membrane)

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	Morning of Admission, Other Hospital, Emergency Department	On Admission, This Hospital	2nd Day
Hematocrit (%)	41.0–53.0 (men)	39.2	35.8	31.0
Hemoglobin (g/dl)	13.5–17.5 (men)	13.7	12.1	10.4
White-cell count (per mm^3)	4500–11,000	7000	6600	4800
Differential count (%)				
Neutrophils	40–70	81	78	76
Lymphocytes	22–44	10	14	16
Monocytes	4–11	9	6	6
Eosinophils	0–8	0	1	1
Basophils	0–3	0	1	1
Erythrocyte count (per mm^3)	4,500,000–5,900,000		3,650,000	3,240,000
Erythrocyte sedimentation rate (mm/hr)	0–13		6	
Sodium (mmol/liter)	135–145	127	124	126
Potassium (mmol/liter)	3.4–4.8	3.0	3.4	2.4
Chloride (mmol/liter)	100–108	87	90	92
Carbon dioxide (mmol/liter)	23.0–31.9	21	20.6	21.0
Anion gap (mmol/liter)	3–15	19	13	13
Bilirubin (mg/dl)				
Total	0.0–1.0		1.3	
Direct	0.0–0.4		0.2	
Protein (g/dl)				
Total	6.0–8.3		5.2	
Albumin	3.3–5.0		2.6	
Calcium (mg/dl)	8.5–10.5		7.8	
Magnesium (mmol/liter)	0.7–1.0		0.7	0.8
C-reactive protein (mg/liter)	<8.0, for inflammation		17.9	
Vitamin B_{12} (pg/ml)	>250			1272

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for vitamin B_{12} to picomoles per liter, multiply by 0.7378.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

measuring 8 mm by 6 mm with exposure of the uvea, as well as a suppurative corneal ulcer adjacent to the perforation temporally that measured 9 mm by 2 mm; the temporal edge of the cornea appeared hazy and edematous, without thinning. Visual acuity measured 20/200 on the right (tested with a visual acuity card held at a specific distance from the patient's face) and was graded as light perception on the left (the patient could not detect hand motion but could tell when a flashlight was turned on or off). The right pupil was 3 mm in diameter, reactive to 2 mm, with no relative afferent pupillary defect; the left pupil was obscured by purulence. Extraocular movements were full. The intraocular pressure in the right eye was 13 mm Hg.

On general physical examination, there were petechiae on the soft palate; follicular horny papules, perifollicular erythema, corkscrew hairs, and nonscarring alopecia on the arms; and perifollicular and nonfollicular purpuric macules and papules on the legs. A mental-status examination revealed lack of insight and a flat affect. The remainder of the examination was normal. The platelet count, red-cell indexes, erythrocyte sedimentation rate, and results of renal-function tests were normal, as were blood levels of glucose, phosphorus, globulin, alanine and aspartate aminotransferases, alkaline phosphatase, and angiotensin-converting enzyme; toxicologic screening was negative. Other laboratory results are shown in Table 1. Blood cultures were obtained.

Dr. Javier M. Romero: Computed tomography (CT) of the head performed with the administration of contrast material revealed multiple subcentimeter rim-enhancing lesions, predominantly in the submental subcutaneous tissue (Fig. 2A); there was substantial fat stranding surrounding these lesions, a feature that most likely represented multiple fluid collections and raised suspicion for microabscesses. There was swelling and fat stranding in the medial canthus of the left globe. There was also left preseptal soft-tissue swelling associated with scleral thickening (Fig. 2B). These findings were compatible with periorbital cellulitis and scleritis. CT of the brain without the administration of contrast material revealed mild soft-tissue swelling and fat stranding overlying the left eye. There was no evidence of acute intracranial hemorrhage, territorial acute infarction, or intracranial mass lesion.

Figure 1. Photograph of the Eye.
A photograph of the patient's left eye, obtained at the time of admission, shows conjunctival injection with purulent crusting and discharge on the eyelashes.

Dr. Heath: Vancomycin, cefepime, magnesium sulfate, potassium chloride, and normal saline were administered intravenously, and folate, thiamine, and a multivitamin were given orally.

On the second day, testing for rheumatoid factor and antibodies to double-stranded DNA, Ro, La, Sm, RNP, and treponema (syphilis) was negative, as was testing for human immunodeficiency virus antibodies and antigen. Other test results are shown in Table 1.

A procedure and diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Melvin S. Blanchard: This patient presented with rapidly progressive vision loss, associated with dry eyes, conjunctival injection, discharge, and corneal melting (progressive stromal dissolution). When a patient presents with acute vision loss, the first assessment should be whether the cause is neurologic or optical.[1] Transient blindness in the family history raises the possibility

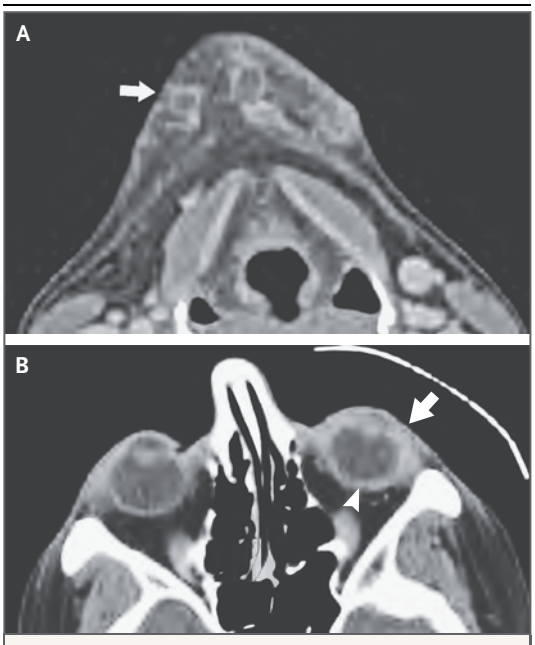

Figure 2. CT Images.
A CT scan of the head obtained with the administration of contrast material shows multiple rim-enhancing cystic lesions in the submental subcutaneous tissue (Panel A, arrow). Fat stranding and swelling of the preseptal soft tissues of the left ocular globe (Panel B, arrow) are noted. The left sclera shows thickening and enhancement (arrowhead), which most likely indicate scleritis.

of vascular disease or embolization. However, symptoms and signs in this patient, including the absence of afferent pupillary defect and the presence of bilateral corneal opacity, strongly suggest an optical cause of vision loss.

CAUSES OF ACUTE LOSS OF VISION

This patient's history provides clues to causes of vision loss. One possibility is keratoconjunctivitis sicca, which usually manifests with red, dry, itchy eyes and a sensation of a foreign body in the eye. Keratoconjunctivitis sicca may be a consequence of Sjögren's syndrome or drugs, including anticholinergic agents or antihistamines. The patient had used tetrahydrozoline, an alpha agonist, as an eyedrop, but he had not taken anticholinergic or antihistaminic medications. Patient's with Sjögren's syndrome present with prominent dry eyes and dry mouth due to autoimmune disease that targets the lacrimal and parotid glands. This patient did not report dry mouth, and the physical examination and the laboratory data did not suggest rheumatic disease. Infectious or noninfectious conjunctivitis can cause red eye, but there is usually a clear or cloudy discharge, which this patient did not notice early in the course of his symptoms. Other possible causes of red eye include blepharitis due to *Staphylococcus aureus*, ocular rosacea, keratitis, scleritis, and episcleritis. The acneiform rash in the patient's history could represent rosacea, which is associated with blepharitis. The patient reported that he had no pain in the eye, and the absence of pain reduces the likelihood that his eye disease is due to keratitis or scleritis, since patients with keratitis or scleritis present with pain, unless there is corneal anesthesia from injury to the fifth cranial nerve bilaterally.

This patient's family history of a "spine fusion disease," most likely ankylosing spondylitis, again raises the possibility of scleritis or peripheral ulcerative keratopathy.[2] However, both of these conditions are associated with eye pain, which the patient did not have.

CONSEQUENCES OF INHALATIONAL DRUG USE

The patient's history of inhalational drug use, although he reportedly had not used such drugs in the 3 months before presentation, adds another possible cause of ocular blindness. The vapors from the inhalation of "crack" cocaine and methamphetamine are toxic to corneal nerves and can lead to corneal anesthesia, decreased blink rate, and consequently, exposure keratopathy.[3] The bacteria in inhalational drugs can also cause infectious keratitis, complicating corneal melting. Inhalational drug use could explain the painless injection of the eyes, the subsequent discharge, and the corneal melting in the left eye.

CORNEAL ULCERS

On examination of the patient's eyes, a suppurative infiltrate and a large corneal ulcer were noted. This raises concern for a number of infectious and noninfectious causes of vision loss and corneal ulcers. The dry eyes on presentation may have put the patient at risk for infection. Since the cornea is an avascular structure, tear fluid is essential to its health. Tear fluid provides immunoactive substances, such as IgA, lysozyme, and lactoferrin, and nourishment of the cornea and protection from infection.[4] A reduction in the amount of tear fluid or a lack of fluid puts the

cornea at risk for infection and ulceration. Bacteria, fungi, viruses, and amoeba can infect the cornea. *S. aureus*, *Streptococcus pneumoniae*, and *Moraxella liquefaciens* are all possible causes of corneal infection in this patient. Patients with herpes simplex virus, the most common cause of corneal ulceration and corneal blindness in the United States, can present with painless corneal ulcers. However, involvement in both eyes is rare.[5] Pseudomonas is associated with contact-lens use, which is not a consideration in this patient. Acanthamoeba, a free-living amoeba, is also associated with the use of contact lenses and exposure to contaminated water. Fungi and mycobacteria, which cause indolent infections, are unlikely in this patient who presented with rapid vision loss. Multiple organisms, including capnocytophaga, *Candida albicans*, and *Strep. mitis*, may also cause corneal ulcers in association with the inhalational drugs used by this patient.[3]

Several noninfectious causes of corneal ulceration warrant consideration in this case. Immune-complex disease affects the periphery of the cornea, close to the limbal capillaries. Peripheral ulcerative keratitis and ulceration can be due to rheumatoid arthritis; the conditions are usually painless, but they occur in the later stages of disease. Other possible causes are systemic lupus erythematosus, scleroderma, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), ulcerative colitis, ankylosing spondylitis, mycobacteria, and treponema, none of which are suggested by this patient's history, physical examination, or serologic studies.[2] Mooren's ulcer and marginal infiltrates tend to be painful, a feature that is not consistent with this patient's history. Neurotrophic ulcers and exposure keratitis are possible but unlikely, given the patient's presentation.

VITAMIN C DEFICIENCY

The patient's general appearance, other aspects of his physical examination, and his social situation raise concern for nutritional deficiencies. He was thin, with bitemporal wasting (BMI, 19.4), was unemployed, and used alcohol and inhalational drugs. He also had poor insight and hoarding behavior, findings suggestive of psychopathology. The physical examination describes corkscrew hairs in areas of the body where they would be unexpected; the examination also describes perifollicular erythema, petechiae, and purpuric macules on the leg, which are pathognomonic for vitamin C deficiency.[6,7] Vitamin C deficiency, or scurvy, well recognized among seamen in the 18th century, is now a rare condition.[8] Today, the risk factors for scurvy include alcoholism, low socioeconomic status, and psychiatric disorders that lead to poor nutrition.[6] This patient's eye problem would not be explained entirely by scurvy, but scurvy may be a clue that he had other vitamin deficiencies.

VITAMIN A DEFICIENCY

This patient had follicular horny papules, which are seen in vitamin A deficiency. This nutritional deficiency causes night blindness, bilateral dry eyes, punctate keratitis, corneal neovascularization, and keratomalacia (corneal melting).[9-13] In addition, vitamin A deficiency causes squamous metaplasia with general hyperkeratinization. When these lesions affect the eye, they appear as white spots, typically on the temporal aspect of the sclera, called Bitot's spots. There is no documentation of night blindness or Bitot's spots in this patient, but other features of vitamin A deficiency are present. However, vitamin A deficiency is rare in the United States. The vitamin is found naturally in many foods, such as green leafy vegetables, carrots, sweet potatoes, tomatoes, cantaloupes, egg yolks, butter, cheese, and liver. Inadequate intake of vitamin A may be due to avoidance of these foods by patients with a psychiatric disorder or a selective diet. Malabsorption of fat-soluble vitamins may also cause vitamin A deficiency. The patient had behavioral symptoms suggestive of a psychiatric disorder, but no symptoms suggestive of malabsorption. In fact, his vitamin B_{12} level was normal, suggesting that the distal small bowel, where both vitamin A and vitamin B_{12} absorption occurs, was intact. His risk factor for vitamin A deficiency would most likely be malnutrition, a factor that is consistent with his vitamin C deficiency. Ocular manifestations of vitamin A deficiency may be exacerbated by hypoproteinemia, which was found in this patient.[14]

In summary, the most likely diagnosis in this patient is xerophthalmia with keratomalacia due to multiple vitamin deficiencies, including vitamins A and C. It is likely that he also has a superimposed infectious keratitis.

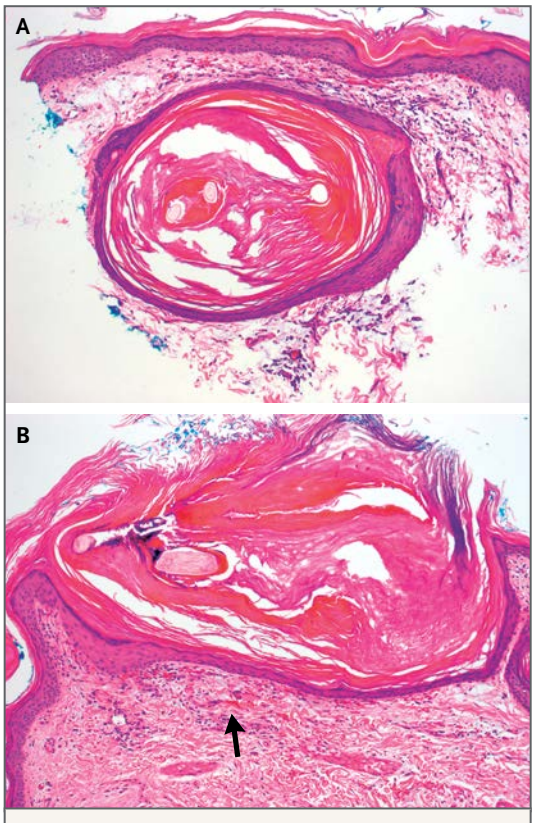

Figure 3. Skin-Biopsy Specimens (Hematoxylin and Eosin).
A skin-biopsy specimen obtained from a lesion on the patient's right thigh shows a prominent follicular keratotic plug (Panel A), a finding suggestive of vitamin A deficiency. A second specimen shows extravasated erythrocytes in the superficial dermis (Panel B, arrow), a finding suggestive of vitamin C deficiency.

Dr. Eric S. Rosenberg (Pathology): Dr. Heath, what was your impression when you evaluated this patient?

Dr. Heath: On the patient's admission, we focused on potential causes that would explain his ocular and dermatologic findings. In addition to consideration of rheumatologic and infectious causes, vitamin deficiencies were considered. Given the findings of corneal melting and corkscrew hairs, our leading diagnosis was multiple vitamin deficiencies.

CLINICAL DIAGNOSIS

Multiple vitamin deficiencies.

DR. MELVIN S. BLANCHARD'S DIAGNOSIS

Xerophthalmia with keratomalacia due to multiple vitamin deficiencies, including vitamins A and C, and secondary infectious keratitis.

PATHOLOGICAL DISCUSSION

Dr. Mai P. Hoang: This patient underwent two skin biopsies of the rash on his right upper leg. In the first biopsy specimen, the stratum corneum showed hyperkeratosis. The follicular infundibulum was markedly dilated by a keratin plug (Fig. 3A). Histopathologically, vitamin A deficiency is characterized by hyperkeratosis and prominent keratotic follicular plugging.[15] Sweat glands may be atrophic and have squamous metaplasia in severe cases.[16] In the other biopsy specimen, hyperkeratosis containing fragmented hair shafts was noted. Extravasated red cells were noted in the superficial dermis (Fig. 3B); this is a characteristic feature of vitamin C deficiency.[17] There may be follicular hyperkeratosis with fragmented and coiled hairs within this keratotic plug.[17] Taken together, these histologic findings are highly suggestive, but not diagnostic, of vitamin deficiency. The next step in the evaluation of this patient was to measure blood vitamin levels. On hospital day 2, his vitamin A level was noted to be less than 2.0 μg per deciliter (0.07 μmol per liter; normal range, 32 to 78 μg per deciliter [1.12 to 2.72 μmol per liter]), his vitamin C level was less than 0.1 mg per deciliter (5.7 μmol per liter; normal range, 0.6 to 2.0 mg per deciliter [34.1 to 113.6 μmol per liter]), and his vitamin D level was less than 3.0 ng per milliliter (7.5 nmol per liter; normal range, >32 ng per milliliter [79.9 nmol per liter]), confirming the diagnosis of multiple vitamin deficiencies.

FOLLOW-UP

Dr. Heath: After the diagnosis was made, the patient underwent vitamin repletion with vitamins A, C, and D.

It was believed that the patient's visual symptoms were caused by severe vitamin A deficiency and corneal scarring, complicated by a super-

imposed infection. Cultures of corneal aspirate revealed a polymicrobial infection, notable for moderate alpha-hemolytic streptococcus, moderate *Eikenella corrodens*, moderate coagulase-negative staphylococcus, moderate *M. catarrhalis*, *Strep. pneumoniae*, and presumptive fusobacterium species. On hospital day 1, he underwent removal of the necrotic cornea of the left eye and subsequent placement of a corneoscleral graft and intravitreal injection of vancomycin, ceftazidime, and amphotericin B. The administration of systemic vancomycin, cefepime, and moxifloxacin was begun, which was changed to moxifloxacin, amoxicillin with clavulanate, and metronidazole for completion of a 3-week course. The dermatologic findings of perifollicular purpura and corkscrew hairs were consistent with profound vitamin C deficiency. The purpuric lesions improved with vitamin repletion during the hospital course. Notably, his flat affect also improved dramatically within 24 hours after vitamin repletion.

The underlying cause of the patient's vitamin depletion was believed to be nutritional. After supplementation, the vitamin A level was 73.3 μg per deciliter (2.56 μmol per liter) and the vitamin C level was 1.2 mg per deciliter (68.1 μmol per liter). Complexities with discharge planning were associated with the patient's vision loss and recent eviction from his apartment; he was eventually discharged, after a 34-day hospital course. At a follow-up appointment in ophthalmology, he was noted to have a visual acuity of 20/40 in the right eye and only hand motion (the patient could not count the examiner's fingers but could detect hand motion) in the left eye. Unfortunately, he was subsequently lost to follow-up.

A Physician: Do you have a sense of what the patient's diet was like?

Dr. Heath: The patient would not reveal his typical daily diet, but notably, he was unable to identify sources of vitamin C, even after education. Unfortunately, he refused evaluation by the nutritionist on multiple occasions. There was concern from his family members that he was hoarding, and his diet was extremely limited.

A Physician: Did the patient's hip pain improve with treatment?

Dr. Heath: Yes, the pain in the hip improved with treatment. The patient underwent additional radiologic studies to further evaluate this symptom, but results of the workup were unremarkable.

A Physician: If the underlying cause of this patient's vitamin deficiency was nutritional, why was his vitamin B_{12} level normal?

Dr. Blanchard: The body is able to store vitamin B_{12} for many years. Vitamin A storage lasts a relatively short time (months), so a much longer period of malnutrition would be required for someone to become deficient in vitamin B_{12}. We do not have any evidence that this patient had liver disease, but if he did, then the period of vitamin A storage would have been even shorter. In terms of his vitamin C deficiency, the storage period is also short, and excretion is increased 40 to 50% in persons who drink alcohol. Therefore, in the short term, the patient had a much greater risk of deficiency in vitamins A and C than in vitamin B_{12}.

FINAL DIAGNOSIS

Severe vitamin A, C, and D deficiencies.

This case was presented at the Medical Case Conference.

Dr. Romero reports receiving payment for board membership at Lundbeck and consulting fees from Lundbeck and Synark. No other potential conflict of interest relevant to this article was reported.

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

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