Erythema Multiforme Exudativum

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Abstract

Erythema multiform is an unusual but potentially serious reaction which develops in a few patients. It is believed to be an immune response to certain drugs or to other stimuli.

The Stevens-Johnson syndrome represents the ocular manifestations when the reaction involves the mucous membranes.

Penicillin has in rare instances precipitated erythema multiforme and requires that those who administer it be aware of this potential and be prepared to treat the patient if such an unwanted development occurs.

Abrégé

Erythème multiforme est une reaction peu commune mais potentiellement sérieuse observée chez un petit nombre de personnes. Il semblerait que la condition est un effet secondaire de quelques médicaments ou autre stimulant.

Le syndrome Stevens-Johnson est une manifestation oculaire de cette réaction quand les membranes muqueuses sont impliquées.

La penicilline peut, en de rares situations, précipiter l'erythème multiforme et exige que le praticien traitant soit averti de cette possibilité et soit prêt à soigner le patient si une telle réaction survenait.

Erythema multiforme is an acute, inflammatory skin disease of uncertain origin[1-4] which occurs mostly in children and young adults especially males.[1,5,6] Other names which have been used are: mucocutaneous-ocular syndrome, eruptive fever-stomatitis-ophthalmia syndrome, dermatostomatitis, ectodermosis erosiva pluriorficialis, mucosal respiratory syndrome, erythema multiforme bullosum. The condition has been confused with Lyell's disease,[1,7] hemorrhagic measles[8], exfoliative dermatitis[7] and herpetic stomatitis[1].

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In the prodromal stage the patient develops malaise and the signs and symptoms usually seen with upper respiratory tract infections.[2,4,8] Fever is usual,[9,10] local lymph nodes become enlarged,[2] joint pain occurs[1] and headache can be severe.[7] The active stage supervenes within one or two weeks with the typical skin and sometimes mucous membrane reactions. The symmetrically distributed skin lesions take the form of macules or papules, followed by bullae and ulcers.[4] Often the lesions become hemorrhagic.[10] The individual lesions are described as annular "iris", target or bull's eye lesions, up to 1 cm in diameter with a clear center surrounded by a red ring.[11] Later the center becomes purple. The rash usually appears first on the body but eventually on the dorsum of the hands and feet as well as on the palms and soles. Some say the rash appears on the hands and feet first.[8] If the reaction continues to worsen the patient becomes quite ill with joint pains, prostration, weak pulse and weakness.[11] In Steven's and Johnson's two original patients, leukopenia was noted.[9] The nails are often affected,[1,7,12] and may be lost. Scaling, a little scarring and minor changes in pigmentation develop later.

In about 25% of cases the mucous membranes become involved and a few develop only the mucous membrane reaction. Inflammation with ulceration and erosion may occur in the mucous membranes of the nose, mouth, throat, rectum, urethra, vagina, penis and conjunctiva.[2,3] From 10 to 20% of those who develop severe reactions die.[7,13]

In the third stage cicatrization and shrinkage of mucous membranes occur but skin pitting does not.

About 2/3 of those with skin involvement develop ocular involvement.[5,12] Among those with mucous membrane involvement over 90% show ocular involvement.[3] Ocular tissue reaction is a feature of the severe form called Stevens-Johnson disease[6] and ocular damage may continue to produce symptoms long after the systemic disease appears to have ended.[2]

The ocular manifestations take the following form:[6,8,12,14]

Catarrhal or purulent conjunctivitis[9,10,15] is an early sign and in severe cases a pseudomembrane forms.[2,7] The conjunctiva develops chemosis, vesicles, bullae and ulcers.[4,16] Secondary bacterial infections are usual. The orifices of the lacrimal glands become occluded so that the conjunctiva becomes dry and keratinized.[3,14] A mucin deficiency[17] and loss of goblet cells[14] is associated with the keratoconjunctivitis sicca. The severe drying requires tarsorrhaphy in many cases.[14] Symblepharon formation is typical.[15] When scarring and shrinkage take place the fornices tend to be obliterated.

The eyelids frequently manifest the skin conditions described above usually with marked edema.[10] The blepharitis is followed by epidermalization of the palpebral conjunctiva. The scarring can result in ectropion or entropion and trichiasis with secondary damage to the cornea. Adhesions between the lids and eyeball are common[3,18] and generally require surgery.

In most cases the cornea develops punctate keratitis followed by superficial pannus, often inferiorly.[19] Vascularization occurs and photophobia is a prominent symptom.[4,8] Ulceration can lead rapidly to perforation and be followed by severe scarring or even by endophthalmitis.[8-10] The cornea suffers keratitis sicca, with epidermalization and often sustains stromal scarring and opacities.[3]

In a few affected eyes anterior uveitis occurs[3] and eyes have been lost from panophthalmitis. Extraocular muscle function is impaired by adhesions between the lids and the eyeball.

Soft contact lenses may help the cornea to heal.[14] Contact lenses help to relieve the pain of keratitis but

should only be fitted in the acute stage if the tear supply is adequate.[14] Scleral lenses have been used to prevent symblepharon formation and loss of the fornices.[5,6,20] Tarsorrhaphy is required to prevent corneal exposure in some eyes.[14] Tear substitutes or supplements are necessary in most cases.[6,13]

Immune, infective and allergic mechanisms have been held to be responsible for erythema multiforme.[1,2,14] Reactions to drugs are frequently implicated[21] and secondary bacterial or viral infections almost always complicate the illness.[8,22] In severe cases blindness or death can result.[9,16,21] Usually the systemic disease is self-limited with its acute stage lasting four to six weeks,[2,4,7], but it may recur year after year in some patients.[1]

Persons most likely to develop erythema multiforme are those with:

— a personal or family history of allergy[7], or asthma[11,13]
— a history of herpes simplex infections[1,2,6,22]
— other recent viral infections,[6,7] or bacterial infections[1,2,7]
— active or latent fungal infections
— recent vaccination[1,6] or deep x-ray therapy[1,7]
— pregnancy[1]
— malignant[6] or chronic disease (e.g.: ulcerative colitis[21]) of the internal organs[1,7,21]

Recently in Toronto a 30-year-old man lost his sight from ertythema multiforme apparently developing as a reaction to penicillin. Although the penicillins are the least toxic of all antibiotics and are effective against most pathogenic cocci they carry the risk of causing an allergic or hypersensitivity reaction. About 5% of the population is allergic to penicillin.[13] Allergic dermatitis develops in 16% of eyes treated with topical penicillin.[24] So penicillin should not be applied topically on the eye.[13] An exception is the use of penicillin against some bacterial corneal ulcers, for example carbenicillin to treat Pseudomonas ulcers of the cornea.

Two types of reaction to penicillin have been reported:

(a) *immediate*

Within minutes the patient develops an anaphylactic reaction[25] with laryngeal edema, angioedema, urticaria and swelling of lips, tongue and periorbital tissues, and goes into shock. Penicillin is the most common cause of anaphylactic shock.[13] Anaphylactoid reactions occur in about 0.025%. A few die promptly. Among those treated with penicillin as many as one in 50,000 are said to die from anaphylaxis. Although these deaths are attributed to penicillin it is likely that some are not due to penicillin itself. Fatalities occur in nine to 13% of those who experience a severe reaction.[13]

(b) *delayed*

The most common reaction[13] is a serum-sickness type which develops within one or two weeks. Affected patients get urticaria, rash, fever, malaise, diarrhea and pains in muscles and joints. While they rarely suffer exfoliation, thrombocytopenia or eosinophilia, a few develop nephritis leading to renal insufficiency. Although they may be ill for weeks, most recover.

Treatment: *

While the responsibility for the administration of drugs for therapeutic purposes is borne by the physician, optometrists need to be familiar with potential effects and able to monitor these patients and discuss their progress with physicians.

Prevention

— penicillin should be used only where appropriate
— it is not used for high risk patients[26], an adequate history should be taken
— it is not applied topically unless absolutely necessary[13]

* The author wishes to emphasize that this treatment procedure is not a therapy to be carried out by the optometrist, but is described herein for the information of the optometrist.

For the immediate reaction:

— be prepared to deal with such a reaction,[26] keep patient in the office for 30 minutes to be sure that an acute reaction is not going to occur away from prompt help.
— give 0.5 ml of 1/1000 epinephrine SC or IM or in severe cases 0.2 to 0.3 ml diluted in 10 ml of saline given slowly IV
— provide oxygen
— make sure the airway is open, this may require insertion of a plastic airway or even tracheostomy
— may need IV fluids eg. 5%

Among the potential causes for erythema multiforme the following drugs have been held to be responsible:[1,3,5-7,11,14,20-23]

acetoaminophen
amithiozone
arsenicals
barbiturates
belladonna derivatives
bromides
carbamazepine
chlorpropamide
chloroquine derivatives
coal-tar derivatives
codeine
cortisone
diphenylhydantoin
gold salts
iodides
meprobamate
mercury
methylphenidate
neoarsphenamine
novobiocin
para-aminosalicylic acid
paramethadione
penicillins
phenacetin
phenolphthalein
phenothiazines
phenytoin
phenylbutazone
propranolol
pyrivinium
quinine
salicylates
succinimide
sulfonamides (one or two cases per million doses of the long-acting sulfas)
sulfur
tetracyclines
thiacetazone
thiazides
thiouracil
tolbutamide
triamethadione
tyrothricin

glucose in water. (A few develop ventricular arrhythmia)
— corticosteroids (with caution),[12] some give antihistamines parenterally eg. 50 mg of diphenhydramine hydrochloride IV.
— some advise use of penicillinase but it can itself cause anaphlaxis[13]. It may be useful against the delayed-type reaction.

Later those who develop a Stevens-Johnson reaction may need:
— antibiotics to control secondary infections[1]
— tarsorrhaphy to decrease the need for tears and to prevent corneal opacification[14]
— contact lenses to protect the cornea from aberrant lashes[6]
— epilation of lashes[6]
— surgery for symblepharon or to correct lid position[6,18,20]
— occlusion of puncta to conserve tears[6,14]
— corneal transplant[27]
— transplant of a parotid duct to the conjunctiva to supply fluid to the conjunctival surface[6]

References

1. Coursin, D.B., Stevens-Johnson syndrome nonspecific parasensivity reaction? *J. Am. Med. Assoc.*, 198: 113-116, 1966.
2. Duggan, J.W., and S.R. Gaines, The ocular complications of erythema exudativum multiforme, *Am. J. Ophthalmol.*, 34: 189-197, 1951.
3. Patz, A., Ocular involvement in erythema multiforme, *Arch. Ophthalmol.*, 43: 244-256, 1950.
4. Jones, W.Y., F.f. Talbot, and W.F. King, Stevens-Johnson's disease, *Am. J. Ophthalmol.*, 29(2): 185-189, 1946.
5. Greenberg, L.M., D.A. Mauriello, A.A. Cinotti and J.N. Buxton. Erythema multiforme exudativum (Stevens-Johnson syndrome) following sodium diphenylhydantoin therapy, *Ann. Ophthalmol.*, 3: 137-139, 1971.
6. Howard, G.M., The Stevens-Johnson syndrome. Ocular prognosis and treatment, *Am. J. Ophthalmol.*, 55(5): 893-900, 1963.
7. Ostler, H.B., M.A. Conant, and J. Groundwater, Lyell's disease, the Stevens-Johnson syndrome and exfoliative dermatitis, *Trans. Am. Acad. Ophthalmol, Otolaryngol.*, 74(6): 1254-1265, 1970.
8. Bailey, J.H., Lesions of the cornea and conjunctiva in erythema exudativum multiforme (Hebra), *Arch. Ophthalmol.*, 6(3): 362-379, 1931.
9. Stevens, A.M., and F.C. Johnson, New eruptive fever associated with stomatitis and ophthalmia, Report on two cases in children, *Am. J. Dis. Child.*, 24: 526-533, 1922.
10. McCurry, A.L., The Stevens-Johnson syndrome, *Trans Ophthalmol. Soc.* UK, 73: 103-109, 1953.
11. Martin, E.W. (Ed.), Hazards of Medication, Philadelphia and Toronto, J.B. Lippincott, 1971, pp. 346-348.
12. Tabbara, K.F., and H.F. Shammas, Bilateral corneal perforations in Stevens-Johnson syndrome, *Can. J. Ophthalmol.*, 10: 514-517, 1975.
13. Hewitt, W.L., The penicillins, *J. Am. Med. Assoc.*, 185: 264-272, 1963.
14. Arstikaitis, M., Ocular aftermath of Stevens-Johnson syndrome, *Arch. Ophthalmol.*, 90: 376-379, 1973.
15. Wheeler, J.M., Destructive purulent ophthalmia accompanying an eruptive fever with stomatitis, *Am. J. Ophthalmol.*, 13(6): 508-514, 1930.
16. Mamelok, A.E., and J. Laval, Stenosis of the lacrimal canals and puncta caused by the Stevens-Johnson syndrome, *Am. J. Ophthalmol.*, 40: 83-86, 1955.
17. Jones, B.D., Prospects in the management of tear-deficiency states, *Ophthalmol.*, 83(4): 693-700, 1977.
18. Mattson, R., and O. Carlberg, Eye lesions and their treatment in the so-called Stevens-Johnson syndrome or ectodermosis erosiva pluriorificalis, *Acta. Ophthalmol.*, 31: 469: 483, 1971.
19. Shapiro, J., Erythema multiforme with monocular involvement, *Am. J. Ophthalmol.*, 67(3): 369-371, 1969.
20. Beyer, C.K., The management of special problems associated with Stevens-Johnson syndrome and ocular pemphigoid, *Ophthalmol.*, 83(4): 701-707, 1977.
21. Cameron, A.J., J.H. Baron, and B.L. Priestly, Erythema multiforme, drugs and ulcerative colitis, *Br. Med., J.*, 2: 1174-1178, 1966.
22. Havener, W.H., Ocular Pharmacology (4th ed.), St. Louis, CV Mosby, 1978, pp. 144-158 and p. 564.
23. Fraunfelder, F.T., Drug-Induced Ocular Side Effects and Drug Interactions, Philadelphia, Lea and Febiger, 1976, pp. 304-306.
24. Noe, C.A., Penicillin treatment of eyelid infections, *Am. J. Ophthalmol.*, 30: 477-479, 1947.
25. Waldbott, G.L., Anaphylactic death from penicillin, *J. Am. Med. Assoc.*, 139: 526, 1949.
26. Patterson, R.W. Jr., and H. Yarberry, Severe drug reactions and their emergency treatment as related to ophthalmology, *Am. J. Ophthalmol.*, 58(6): 1048-1054, 1964.
27. Wolff, J.E., Ocular complications in erythema multiforme with mucous membrane lesions, *Br. J. Ophthalmol.*, 33: 110-120, 1949.