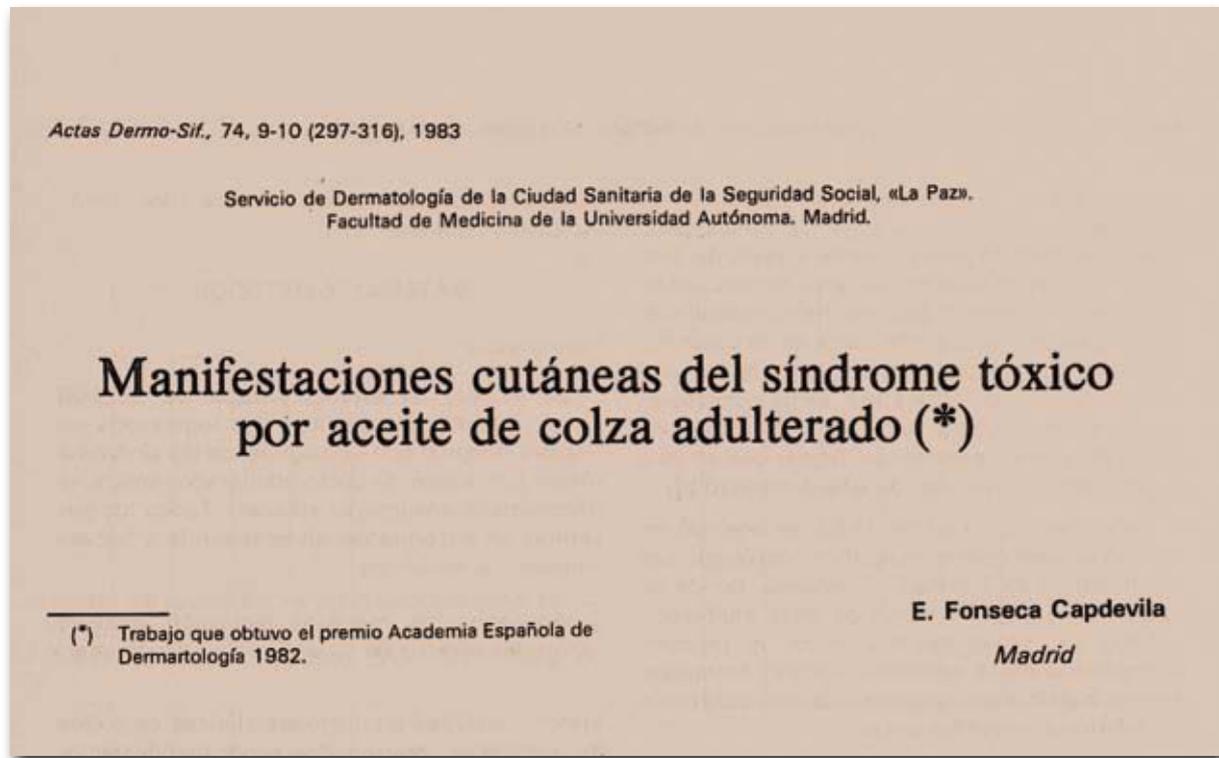


Skin Manifestations of Toxic Syndrome Due to Denatured Rapeseed Oil

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Abstract. This article offered an extensive description of the clinical and pathological features and time-course of the skin manifestations of toxic syndrome caused by denatured rapeseed oil, also known as toxic oil syndrome. This new condition occurred in Spain in 1981 and was due to the ingestion of rapeseed oil intended for industrial use that had been denatured with anilines and subsequently refined and sold fraudulently as olive oil.

In total, 20 000 cases and 400 deaths were reported. The disease affected mainly women, particularly in the late stages. In the acute phase, the predominant skin manifestations were toxic-allergic rashes reminiscent of allergic urticaria in the dermatopathologic study. In approximately 25% of cases, the patients' skin subsequently took on an edematous appearance, with pigmentary abnormalities shown to be related to cutaneous mucinosis. Finally, a characteristic sclerodermatous condition would develop that tended to improve spontaneously. The constant presence of mast cells in all biopsies and the development of mastocytosis in several patients pointed to an important role for these cells in the pathogenesis of the condition. This was subsequently confirmed in other sclerodermatous processes.

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In 1989, eosinophilia-myalgia syndrome caused by toxins present in tryptophan food supplements was reported in the United States. This syndrome resembled toxic oil syndrome in many ways and demonstrated that mucinosis and toxic sclerodermatous processes do exist.

Key words: toxic syndrome caused by denatured rapeseed oil, toxic oil syndrome, rash, mucinosis, toxic mucinosis, sclerodermatous syndrome, scleroderma, eosinophilic fasciitis, eosinophilia-myalgia syndrome, mast cell, mastocytosis.

MANIFESTACIONES CUTÁNEAS DEL SÍNDROME TÓXICO POR ACEITE DE COLZA ADULTERADO

Resumen. En este artículo se efectuó una amplia descripción clínico-patológica y cronológica de las manifestaciones cutáneas del síndrome tóxico por aceite de colza adulterado o síndrome tóxico por aceite. Esta nueva enfermedad se produjo en España en 1981, debida a la ingesta de aceite de colza destinado a uso industrial, que había sido coloreado con anilinas y posteriormente decolorado de forma fraudulenta y vendido como aceite de oliva.

En total se produjeron unos 20.000 casos y unos 400 fallecimientos. Existía un predominio por el sexo femenino, sobre todo en la fase tardía. En la fase aguda las manifestaciones cutáneas predominantes fueron exantemas toxoalérgicos, con un patrón dermatopatológico de erupción alérgica urticariforme. Alrededor de un 25 % de los casos desarrolló posteriormente un aspecto edematoso de la piel, con trastornos de la pigmentación, que demostró estar relacionado con mucinosis dérmica. Finalmente se produjo un cuadro esclerodermiforme peculiar, que tendió a mejorar de forma espontánea. La presencia constante de mastocitos en todas las biopsias y el desarrollo de mastocitosis en varios pacientes sugirieron un papel importante del mastocito en la patogenia del cuadro, que luego ha sido ratificada en otros procesos esclerodermiformes.

En 1989 apareció en EE.UU. el síndrome mialgia-eosinofilia, relacionado con sustancias tóxicas presentes en suplementos alimentarios de triptófano y que compartía muchos aspectos con el síndrome tóxico por aceite. Esto corroboró la existencia de mucinosis y cuadros esclerodermiformes de origen tóxico.

Palabras clave: síndrome tóxico por aceite de colza adulterado, síndrome tóxico por aceite, exantema, mucinosis, mucinosis tóxica, síndrome esclerodermiforme, esclerodermia, fascitis eosinofílica, síndrome mialgia-eosinofilia, mastocito, mastocitosis.

Comment

Toxic oil syndrome caused by contaminated rapeseed oil, also known simply as toxic oil syndrome, was a food-toxin-induced disease that appeared in Spain in 1981. The cause was the ingestion of rapeseed oil that had been imported for industrial uses and to which aniline compounds had been added to color the oil in order to discourage human consumption. The coloring was subsequently removed by means that have never been clarified and the product then fraudulently sold as olive oil under no brand name, usually in 5-L bottles at itinerant markets by traveling vendors. Some was also bottled under brand names and distributed at more conventional commercial outlets.

The first cases were detected near Madrid, in Torrejón de Ardoz and neighboring towns. Initially called atypical pneumonia because of its most salient manifestation, the disease was considered potentially contagious and attributed at first to *Legionella* species infection and later to *Mycoplasma* species.

The clinical features of the syndrome, the absence of contagion in the hospital, and the lack of response to antibiotics but good response to corticosteroids suggested a possible toxic cause. This was confirmed when Tabuenca¹ observed that symptoms were associated with ingestion of denatured rapeseed oil.

The news spread through the mass media with warnings against consumption of oils of unknown origin. As fraudulent brands were removed from the chain of distribution and exchanged for some other type of good-quality oil, the appearance of new cases subsided. The specific toxin responsible for the syndrome, however, has never been identified, and this has given rise to multiple theories about other agents, conspiracies, chemical or biological weapons test accidents, and the like.²

New cases ceased to appear only after it was clear that a genuine emergency health crisis had developed, greatly straining hospital services in Madrid and other parts of Spain. In all, some 20 000 cases are estimated to have occurred and the death toll reached at least 400.

The course of toxic oil syndrome had 2 phases. An acute phase, observed nearly exclusively in May and June 1981, lasted 3 to 4 weeks and was characterized by high fever, cough, dyspnea, headache, skin lesions, pruritus, joint pain, gastrointestinal symptoms, lymphadenopathy, hepatomegaly, noncardiogenic pulmonary edema, and eosinophilia.³⁻⁶ A later phase then occurred in around 25% of the patients, particularly in women. The most important manifestations of this phase were asthenia, weight loss, peripheral neuropathy, muscle atrophy, myalgia, pulmonary hypertension, liver disease, xerostomia, skin lesions, thromboembolism, impaired esophageal motility, and psychological and sleep disorders.³⁻⁶ These manifestations began to emerge in July 1981. The clinical course for most patients was satisfactory and symptoms generally resolved during 1982, although some patients suffered diverse sequelae.^{3,4}

The main histopathologic finding was nonnecrotizing vasculitis affecting mainly the intima of vessels in multiple organs, sometimes accompanied by fibrosis.^{3-5,7} Most deaths during the acute phase were due to respiratory failure secondary to pleuropneumonia; deaths in the later phase were due to thromboembolism, to infectious complications, and again, to respiratory failure.⁷

Hospital La Paz, in Madrid, where I worked in 1981, was one of the main centers responsible for treating patients with toxic oil syndrome due to contaminated rapeseed oil. Several wards were given over exclusively to these patients in order to cope with the problem.

The article published in *Actas Dermo-Sifilográficas* summarized the largest study of cutaneous involvement in this syndrome that was undertaken at the time. It included a prospective analysis of 100 acute-phase cases selected randomly from among patients admitted to Hospital La Paz. The study included epidemiologic data, general medical and cutaneous signs and symptoms, and laboratory and radiologic findings. A purpose-designed questionnaire was used to collect data, and 14 skin biopsies were obtained from 11 patients.

Fifty-five percent of the acute-phase patients were women and 70% developed skin lesions, which were already evident during the first week in 92% of the cases. The most common sign was maculopapular exanthems (in 64% of the cases). Next most common were intense facial edema (36%), urticaria-angioedema (10%), purpura (5%), and oral aphthous ulcers (4%). Sixty percent of the patients complained of pruritus. These manifestations tended to resolve within 2 weeks, and response to treatment with antihistamines and corticosteroids was good.

Histopathologic examination consistently revealed nonnecrotizing endothelial swelling in capillaries and venules, dermal edema, and perivascular infiltrates (mainly lymphohistiocytic but with the additional presence of neutrophils, plasma cells, mast cells, and eosinophils,

occasionally in abundance). Red blood cell extravasation occurred frequently. Direct immunofluorescence was negative in the 2 cases in which this test was carried out.

We interpreted the manifestations of this phase to be toxic-allergic exanthems with a dermal histopathologic pattern consisting off an urticaria-like allergic rash.

Patients could not be selected randomly for analysis during the late phase of the syndrome, but we continued to prospectively study those who were referred for assessment of related skin lesions. Forty-two such cases were studied between July 1981 and November 1982, with 22 biopsies taken from 19 of these patients. Eighty percent were female.

Late-phase skin lesions, which began to appear between June and October 1981, were characterized by pitting edema, a doughy consistency, and were mainly located on forearms, upper arms, calves, and thighs. Whitish papules measuring 1 to 5 mm were present and did not tend to coalesce. Within a few weeks, hyperpigmented maculae 0.5 to 1 cm in diameter developed alongside areas of hypopigmentation. These lesions were associated with mucinosis given that all biopsies carried out between July and November 1981 stained weakly for nonsulfated mucopolysaccharides, with deposits found in the interstitial spaces of the dermis. Perivascular and occasionally perineural infiltrates also persisted in the dermis or were diffusely distributed. These were similar in composition to those of the acute phase, although there was less marked presence of eosinophils and nonnecrotizing vasculitis in capillaries of the dermis and venules of the dermal-hypodermal junction.

By the end of 1981, nearly all these patients had developed scleroderma-like lesions, located mainly in the vicinity of earlier cutaneous changes. Affected skin was sclerous, hard to the touch, nonpitting, and shiny. Adjacent hyper- and hypopigmented patches were present. Fifty-five percent of patients also reported pruritus during this phase. The scleroderma-like lesions were at their most severe between January and February of 1982, after which they improved gradually although the skin continued to be dry, shiny, and hairless. Variations in pigmentation persisted. The various treatments tried during this phase did not lead to significant improvement.

Histopathologic changes noted were epidermal thinning and the presence of dense collagen fibrils in the reticular dermis forming thick, acidophilic bundles. Below the sweat glands a thick layer of dense, disorganized connective tissue formed. Dermal septa were thickened and fibrosing, changes that extended deep into the fasciae. Sweat glands appeared atrophied. Pores were often hyalinized and were sometimes fully separated from the glands.

Four patients developed cutaneous mastocytosis in the form of urticaria pigmentosa. Transient alopecia and sicca syndrome were also noted during this phase.

The report of these cases, featured in this summary, also called attention to a case of multiple plaque morphea observed in 1982. Later we were able to study patients with this syndrome who developed other scleroderma-like conditions such as single plaque morphea, linear morphea, pseudobullous morphea, and eosinophilic fasciitis.⁴ Years later, Díaz Pérez et al⁸ described 3 cases of eosinophilic fasciitis. The patients all belonged to a single family and their symptoms may have been related to toxic oil syndrome.

The pathologic and clinical features of the disease, the persistent presence of mast cells in biopsies, and the observation of several cases of mastocytosis led us to propose that mast cells may play an important pathogenic role throughout the course of the syndrome. Later, numerous studies suggested that mast cells are indeed involved in diverse scleroderma-like syndromes and functional fibroblastic disorders.^{4,9,10}

From the beginning, toxic oil syndrome due to contaminated rapeseed oil was regarded as a new disease, both from a general medical perspective and a dermatologic one. This view has persisted over time. Because we treated a large number of cases in a single hospital, we were able to describe skin lesions and their development in great detail, in spite of limited resources.

Another new condition known as eosinophilia-myalgia syndrome was reported in 1989 in the United States and attributed to the ingestion of poorly manufactured tryptophan diet supplements. More than 1500 cases were registered and 30 people died in that country, though other countries were scarcely affected. Toxic oil syndrome due to contaminated rapeseed oil and eosinophilia-myalgia syndrome share many features, particularly their cutaneous manifestations,¹¹ and with the appearance of the second syndrome interest in the earlier one revived.^{4,12} The 2 entities differed considerably, however, particularly with respect to respiratory symptoms and radiologic signs in the acute phase.

An important lesson learned from toxic oil syndrome due to contaminated rapeseed oil—a lesson that was confirmed by the appearance of eosinophilia-myalgia syndrome—was that a clinical picture involving mucinosis¹³⁻¹⁵ and fibrosclerosis^{9,16} developed in reaction to chemical agents. Toxic mucinosis has been proposed to refer generally to mucinoses arising in such circumstances.^{14,15} The group of scleroderma-like conditions caused by toxic reactions has recently grown larger with the addition of nephrogenic systemic fibrosis (or nephrogenic fibrosing dermopathy) triggered by gadolinium-based contrast agents used in

nuclear magnetic resonance imaging in patients with kidney failure.¹⁷

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