JGG 2018;66:158-162

Drug hypersensitivity cutaneous diseases in the elderly

R. Buquicchio[1], E. Boni[2], S. Procoli[3], G. Serviddio[4], M.T. Ventura[3]

[1] Dermatological Clinic, Department of Biomedical Science and Human Oncology, Medical School, University of Bari "A. Moro", Bari, Italy; [2] Allergy Unit, Hospital Santo Spirito Casale Monferrato (AL), Italy; [3] Department of Interdisciplinary Medicine, Medical School, University of Bari "A. Moro", Bari, Italy; [4] Institute of Internal Medicine, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy

The worldwide increase of life expectancy, changes in immunological capacity, comorbidities and polytherapy are responsible for the increasing prevalence of geriatric drug related allergic skin diseases. In the elderly other factors contribute to the onset of these phenomena, such as changes in the structure of the skin and mucous tissues. The integrity of the epithelial barrier in old people is compromised by the loss of its constituents, that predisposes to alterations of the hydrolipidic film with dryness, xerosis and pruritus. Also at the skin level are frequently found abnormal immunological reactions towards new antigens and a chronic inflammatory state that predisposes to a response oriented towards the Th2 cytokinic pattern, allowing allergens to penetrate into tissues. Nevertheless, in the elderly drug related allergic disorders, in particular at the skin level, are often underdiagnosed and difficult to treat.

Among the IgE mediated cases, urticaria and angioedema are frequent. However, there are also cell-mediated mechanisms; in particular delayed type reactions to drugs often arise in the elderly for the reiterate use of topical medications (anesthetic, antibiotic and anti-inflammatory creams).

A detailed anamnestic history is essential to establish the causal link between an adverse drug reaction and the specific drug. Moreover, in some cases it is necessary the specific knowledge of the histological picture.

Key words: Drug allergy, Drug hypersensitivity, Elderly

INTRODUCTION

During senescence important changes contribute to the fragility of the elderly skin. In particular, the production of type 1 collagen is reduced during senescence; its reduction is responsible for the skin thinning and for the worsening of skin functions. Fibroblasts present an alteration in the spread due to the fragmentation of the collagen fibers, secondary to an increase in the synthesis of prostaglandin E2 [1].

The decrease in the activity of fibroblasts can also be responsible for the elasticity rupture of the elderly skin that appears atrophic, with thinning of the dermal papillae, also due to the loss of hydration and to the changes in the blood flow; it can also lead to the reduced production of sebum, sweat glands atrophy and immune responses modification [2].

Therefore aged skin appears atrophic, with notes of dryness, fragility, alterations in pigmentation, roughness and greater tendency to xerosis. These factors affect the health conditions of the elderly skin, with a marked increase in infectious, autoimmune or neoplastic diseases. In addition, these anatomical and functional changes in the skin district predispose to the appearance of cutaneous drug allergic diseases [3 4].

In the elderly the skin becomes particularly sensitive to the action of the sun rays with consequent increase of erythema, photo-dermatitis or photo-contact dermatitis and neoplastic skin lesions.

Photosensitivity phenomena in the elderly are particularly

Received: June 29, 2018 - Accepted: September 17, 2018

Correspondence: Elisa Boni, Hospital Santo Spirito, ASL Alessandria, viale Giovanni Giolitti 2, 15033 Casale Monferrato (AL) - E-mail: boni6055@gmail.com

relevant for the frequent use of drugs. In fact, phototoxic reactions may occur after intake of common orally administered drugs such as diuretics, cardiac agents and antidiabetics. Photo-contact dermatitis is due to perfumes and other agents contained in topical medications used by the elderly. Actinic dermatitis, the most disturbing disorder of this type, should be reported [5].

Hypersensitivity drug reactions (type B) can be classified, depending on the timing of the reaction, as immediate and delayed. Conventionally, immediate drug reactions occur within one hour after drug intake but may occur also several hours after the exposure. Delayed reactions occur more than 24 hours after exposure. The different time of onset generally implies different pathogenic mechanisms. Non-life-threatening cutaneous adverse drug reactions are frequent and include allergic contact dermatitis (ACD), urticaria, macopapular exanthema/morbilliform eruptions, photo-distributed drug reactions, fixed drug eruptions [6].

CUTANEOUS ADVERSE DRUG REACTIONS

Allergic contact dermatitis

The alteration of the barrier function is responsible for the onset of ACD, an inflammatory dermatitis, intensely itchy, characterized by erythemato-vesicular lesions with a tendency to desquamation or to lichenification. Controversial is the datum concerning the number of Langerhans cells, although, more frequently in the literature it is reported that their percentage would not decrease in senile age. Above all CD4+ and CD8+ lymphocytes seem to contribute to the immune response immunology in the ACD with IL-17 production and lymphocytic infiltrate at the site of the lesion. In the elderly the main haptens responsible for ACDs are nickel, perfume and balsam of Peru in addition to topical medications, including antibiotics, anti-inflammatory ointments, anesthetics and corticosteroids, frequently used for the treatment of skin ulcers or other skin diseases. It is always advisable to perform targeted allergy tests using patch test indicated by national or regional medical societies (e.g. SIDAPA series). Differential diagnosis must be addressed to other dermatology diseases including scabies, seborrheic dermatitis, psoriasis, stasis dermatitis and atopic dermatitis [7 8].

Urticaria

Few studies have examined the prevalence of hives in the elderly and the causes that more frequently support the appearance of urticaria. Furthermore, nowadays there are no specific protocols for the diagnosis and the treatment of urticaria in the subjects over 65 years old. With particular reference to EAACI/GA2LEN/EDF/WAO guidelines hives are distinct as “acute” and “chronic” and classified as “spontaneous” or “induced” depending on whether it manifests itself spontaneously or it is caused by inducible stimuli. Cutaneous lesions are characterized by the transient appearance of smooth, slightly elevated plaques (wheals), intensely itchy and sometimes associated with angioedema. When etiology is not identified, diagnosis of chronic spontaneous urticaria (CSU) is made.

In general, the pathogenesis of CSU is difficult to detect, also if a percentage between 0.5 and 1% suffers from CSU and at least a quarter of the population has experienced hives during its lifetime. It occurs more frequently in the female sex with an incidence equal to about double. In turn, acute urticaria is a clinical manifestation of immediate drug hypersensitivity reactions.

Some authors [9 10] take into consideration the possible correlation between urticaria-angioedema syndrome, comorbidity and polypharmacy in elderly population and reports that in this range of age urticaria is more tied to some internist pathologies including autoimmune diseases, neoplasms, immune-proliferative diseases, diabetes and thyroid disorders. Moreover, in the elderly population the incidence of urticaria is greater if patients take a number of drugs higher than three. This last aspect is related to the degranulation of mast cells induced by drugs, both with immunological and non-immunological mechanisms and to the changes in pharmacokinetics related to age, especially in patients who take drugs that block angiotensin receptors [11-13].

Non-steroidal anti-inflammatory drugs (NSAIDs) are responsible for a large spectrum of hypersensitivity reactions and are considered the first or second cause of hypersensitivity reactions to drugs. Acute skin diseases induced by NSAIDs comprise: i) NSAIDs-exacerbated cutaneous disease (NECD) induced by aspirin or other NSAIDs manifesting as wheals and/or angioedema occurring in patients with a history of chronic spontaneous urticaria; ii) NSAIDs-induced urticaria/angioedema (NIUA): induced by NSAIDs manifesting as wheals and/or angioedema occurring in subjects without history of chronic spontaneous urticaria; iii) Single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA) that is an immediate hypersensitivity reactions to a single NSAID or to several NSAIDs belonging to the same chemical group, manifesting as urticaria, angioedema and/or anaphylaxis. NECD and NIUA are determined by ciclo-oxigenase 1 inhibition while SNIUAA is considered an IgE-mediated reaction [14] (Fig. 1).

Angioedema

Regarding angioedema, also defined as Quincke’s angioneurotic angioedema, it is generally drug-dependent in the elderly patients. There are many drugs that can play a role, including NSAIDs, angiotensin converting enzyme inhibitors (ACEis), radiocontrast means, angiotensin II

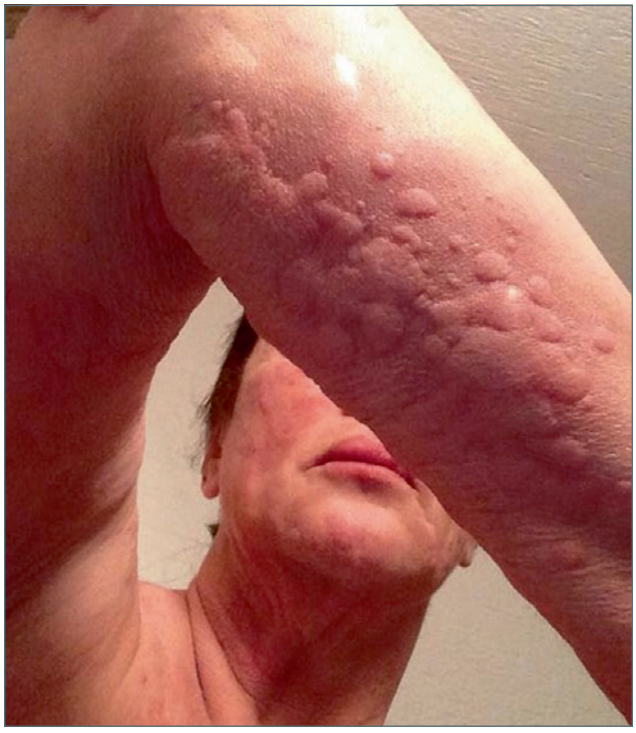

Figure 1. Generalized urticaria induced by ibuprofen intake.

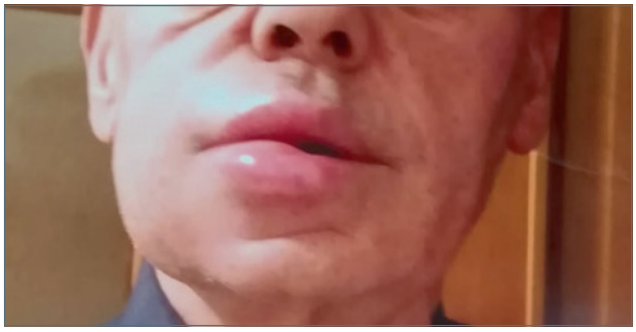

Figure 2. Angioedema of the lips induced by enalapril intake.

receptor antagonists, antibiotics, proton pump inhibitors, statins, fibrinolytic agents, estrogens, diuretics, calcium antagonists, beta blockers and psychotropic drugs (serotonin reuptake inhibitors).
Angioedema may occur in 0.1 to 0.7% of treated patients. It affects the head, neck, face, lips, tongue and larynx with potentially lethal upper airway edema. It can also be resistant to treatment and be fatal (Fig. 2).
The mechanism in patients taking ACEi is due to ACE inhibition, which blocks the conversion of angiotensin, reduces the bradykinin catabolism and increases its activity. The decreased activity of aminopeptidase P and dipeptidyl peptidase P in the degradation pathways of substance P also seems to play a role.

Acquired C1 inhibitor deficiency (AAE-C1-INH) can occur in older patients and it is due to the activation of the classic pathway of the complement system accelerated by the catabolism of C1-INH due to neoplasms of lymphatic tissue or autoimmune diseases.
The prevalence of angiotensin converting enzyme inhibitor of angioedema (AE-ACEi) is relatively high, between 0.1-2.2% and should be suspected in all patients with AE who are receiving ACEi. Normal levels of complement factors help to strengthen the clinical suspicion and to exclude the possibility of AE with C1-INH deficiency. These data suggest that in these cases a careful evaluation of the patient's drug therapy should be encouraged (especially for aspirin and ACEi), besides the evaluation of autoimmune or neoplastic diseases [15].

Exantematous, morbilliform or maculopapular eruptions

These clinical entities represent 95% of all cutaneous drug eruptions. Their clinical features consist of erythematous papules and macules than can become confluent and widespread. Low fever, mild eosinophilia and pruritus can be present. It generally occurs 4-14 days after drug discontinuation. The onset may be faster in previously sensitized patients.

Fixed drug eruption

The clinical presentation is an unique itchy, round, well-circumscribed, erythematous macule or dusky plaque on the skin or on the mucosal surfaces (Fig. 3). Infrequently a small number of macules can be present. The lesions recur on the same area in case of re-exposure to the same offending drug. It is generally benign with the exception of the uncommon severe generalized bullous subtype [6].

SEVERE CUTANEOUS ADVERSE REACTIONS (SCARS)

SCARs encompass several hypersensitivity drug reactions and are mediated by type IV reactions according to Gell and Coombs classification. They include Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reactions with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP).
Most common offenders are allopurinol (the highest agent in Europe, China and USA), aromatic anticonvulsivants, antibiotics, sulphonamides and oxicam NSAIDs [6].
Stevens-Johnson syndrome/toxic epidermal necrolysis
This spectrum of conditions is one of the most common among SCARs (prevalence 1-7 per million) and is associated with high mortality (up to 40%). It is characterized by cutaneous detachment, blisters, necrosis and erosive

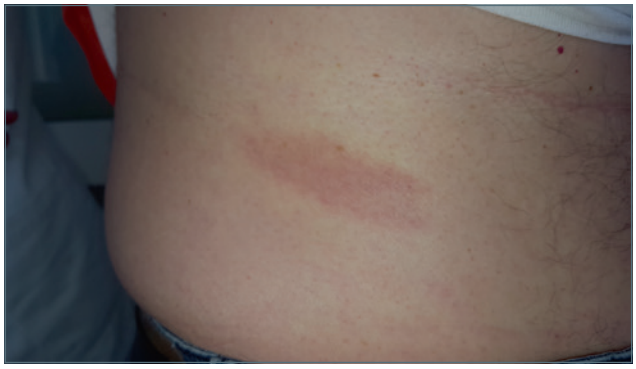

Figure 3. Fixed drug eruption.

mucositis of more than 2 districts. It can be preceded by macules and widespread flat target lesions. Early painful erythema of palms and feet is a typical feature. Fever and influenza-like symptoms may be present. In SJS the affected skin area is less then 10%, in TEN the detachment involves more than 30%. In between lies the SJS/TEN overlap syndrome [6 16]. The onset is usually 4-28 days after the start of the offending drug [17].

Erythema multiforme mayor is usually associated to viral infections and only a minority of cases seems to be associated with drug reactions. It differs from SJS/TEN for the distribution of target lesions which affect acral areas (Figs. 4-5). Chronic kidney disease and the use of diuretics is associated with an increased risk of allopurinol-induced SJS/TEN. Liver disease and HIV infection may be a risk factor of SJS/TEN. A recent Portuguese study observed a significant association between in-hospital mortality consequent to SJS/TEN and advanced age and liver disease. In this study the median age of the affected patients was 63 years and the main drug classes responsible of SJS/TEN were antibiotics, uric metabolism drugs, anticonvulsivants and antivirals. Moreover, advanced age is a risk factor included in SCORTEN (SCORe of Toxic Epidermal Necrosis) severity scale [16].

Drug reactions with eosinophilia and systemic symptoms

DRESS is one of the most common SCARs with an estimated prevalence of 1-4 per million. The eruption is most commonly urticaria-like or an exanthema. The onset is usually 2-6 weeks after the initiation of drug therapy. Fever, facial and acral edema, lymphadenopathy, leucocyte abnormalities (leukocytosis, eosinophilia and/or atypical lymphocytosis), hepatitis, non erosive mucositis, nephritis, pancreatitis, pneumonitis and myocarditis have been reported. It can be associated with reactivation of human herpesvirus-6 and -7 and Epstein-Barr virus. Advanced age and renal failure are risk factors for DRESS. Mortality rate is estimated at 10% [6].

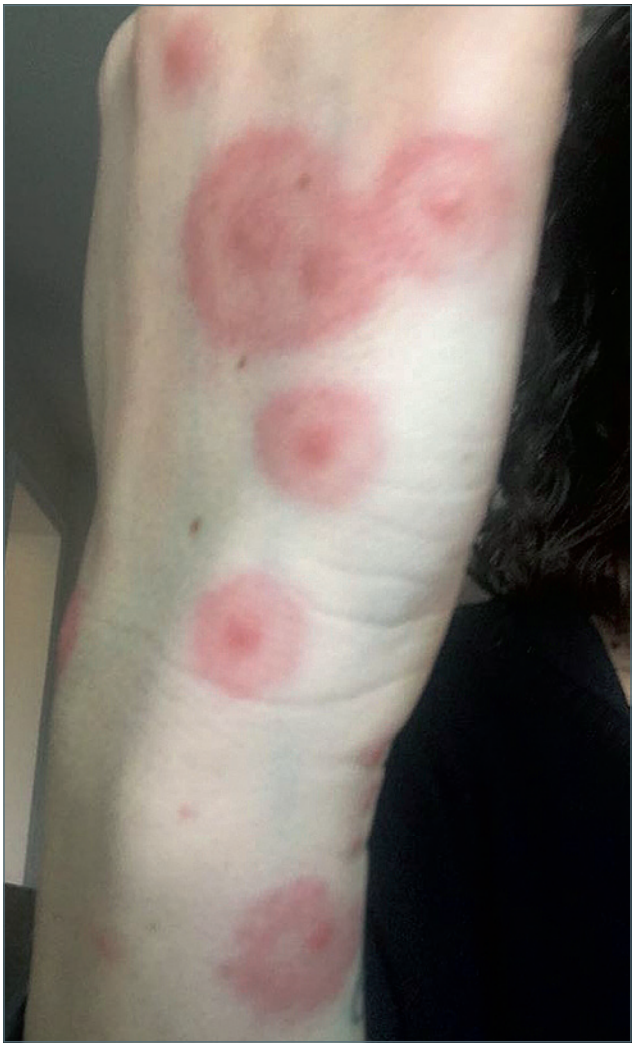

Figure 4. Erythema multiforme mayor associated to viral infections.

Acute generalized exantematous pustulosis

Non-follicular, sterile pustules and erythema are typical clinical signs of AGEP. Mucosal surfaces are also involved in 20-25% of patients with AGEP. It may include fever, leukocytosis, neutrophilia, eosinophilia and hypocalcemia, hepatitis, renal insufficiency and respiratory distress. The onset is typically 1-2 days after the start of the offending drug. Its prevalence is estimated 0.35-5 per million. Mortality is lower than 5% [17].

CONCLUSIONS

In conclusion, drug allergic reaction at skin level is an emerging problem in geriatric age. The structural changes in old cutaneous physiology can favor the onset of atopic dermatitis, ACD, urticaria and angioedema. Furthermore,

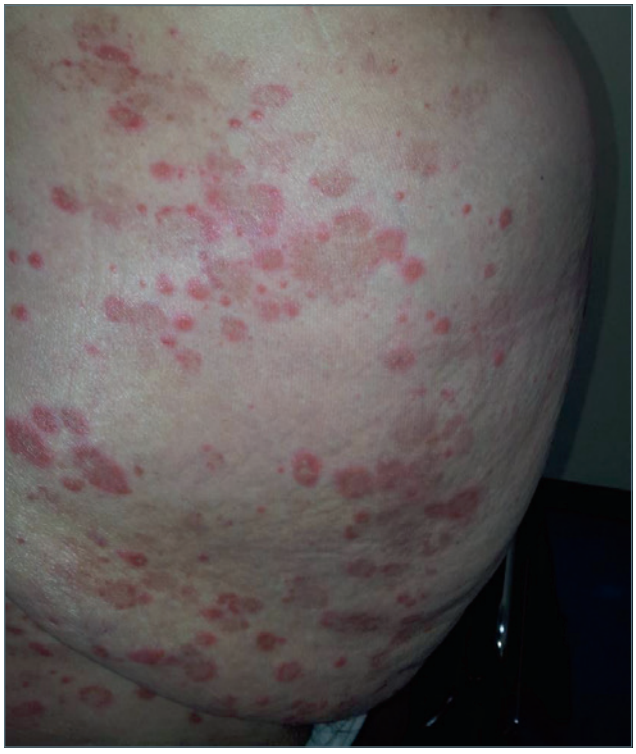

Figure 5. Target lesions induced by drug intake.

the use of numerous drugs and immune system modifications predispose to drug-induced adverse reactions, the incidence of which is directly correlated with the number of pathologies that elderly people are suffering from [18]. "Danger signs" of delayed cutaneous drug reactions are intense facial involvement, atypical target or bullous lesions, epidermolysis, hemorrhagic necrotizing lesions, purpura, widespread dark-red erythema, extensive pustulosis, painful skin, mucosal involvement, generalized lymphoadenopathy, epatopathy, nephropathy [19]. Management of drug hypersensitivity reactions include prompt diagnosis, removal of the culprit drug and early treatment.

Conflict of Interest

All authors have no conflict of interest according to the content of this manuscript.

References

1 Li Y, Lei D, Swindell WR, et al. *Age-associated increase in skin fibroblast-derived prostaglandin E2 contributes to reduced collagen levels in elderly human skin*. J Invest Dermatol 2015;135:2181-8.

2 Farage MA, Miller KW, Berardesca E, et al. *Clinical implications of aging skin: cutaneous disorders in the elderly.* Am J Clin Dermatol 2009;10:73-86.

3 Ventura MT, Scichilone N, Paganelli R, et al. *Allergic diseases in the elderly: biological characteristics and main immunological and non-immunological mechanisms.* Clin Mol Allergy 2017;3:15:2

4 Ventura MT, Scichilone N, Gelardi M, et al. *Management of allergic disease in the elderly: key considerations, recommendations and emerging therapies.* Expert Rev Clin Immunol 2015;11:1219-28.

5 Hawk JL. *Photosensitivity in the elderly.* Br J Dermatol 1990;122(Suppl 35):29-36.

6 Peter JG, Lehloenya R, Dlamini S, et al. *Severe delayed cutaneous and systemic reactions to drugs: a global perspective on the science and art of current practice.* J Allergy Clin Immunol Pract 2017;5:547-63.

7 Balato A, Balato N, Costanzo L, et al. *Contact sensitization in the elderly.* Clin Dermatol 2011;29:24-30.

8 Cardona V, Guilarte M, Luengo O, et al. *Allergic diseases in the elderly.* Clin Transl Allergy 2011;1:11.

9 Ventura MT, Napolitano S, Buquicchio R, et al. *An approach to urticaria in the elderly patients*. Immunopharmacol Immunotoxicol 2012;34:530-3.

10 Ventura MT, Cassano N, Romita P, et al. *Management of chronic spontaneous urticaria in the elderly*. Drugs Aging 2015;32:271-82.

11 Zuberbier T, Asero R, Bindslev-Jensen C, et al. *EAACI/GA(2) LEN/EDF/WAO guideline: management of urticaria*. Allergy 2009;64:1427-43.

12 Kaplan AP, Greaves M. *Pathogenesis of chronic urticaria*. Clin Exp Allergy 2009;39:777-87.

13 Magen E, Mishal J, Schlesinger M. *Clinical and laboratory features of chronic idiopathic urticaria in the elderly.* Int J Dermatol 2013;52:1387-91.

14 Kowalski ML, Asero R, Bavbek S, et al. *Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs*. Allergy 2013;68:1219-32.

15 Malde B, Regalado J, Greenberger PA. *Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers*. Ann Allergy Asthma Immunol 2007;98:57-63.

16 Sousa-Pinto B, Araújo L, Freitas A, et al. *Stevens-Johnson syndrome/toxic epidermal necrolysis and erythema multiforme drug-related hospitalisations in a national administrative database.* Clin Transl Allergy 2018;8:2.

17 Demoly P, Adkinson NF, Brockow K, et al. *International Consensus on drug allergy.* Allergy 2014;69:420-37.

18 Ventura MT, Boni E, Cecere R, et al. *Importance of hypersensitivity in adverse reactions to drugs in the elderly.* Clin Mol Allergy 2018;16:7.

19 Scherer K, Bircher AJ. *Danger signs in drug hypersensitivity.* Med Clin North Am 2010;94:681-9.