Drug-induced peripheral edema: an etiology-based review

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Abstract

Many drugs are responsible, through different mechanisms, for peripheral edema. Severity is highly variable ranging from slight edema of the lower limbs to anasarca pictures as in the capillary leak syndrome. Although most often non-inflammatory and bilateral, some drugs are associated with peripheral edema that is readily erythematous (e.g., dopaminergic agonists, pemetrexed) or unilateral (e.g., sirolimus). Thus, drug-induced peripheral edema is underrecognized and misdiagnosed, frequently leading to a prescribing cascade. Four main mechanisms are involved, namely precapillary arteriolar vasodilation (vasodilatory edema), sodium/water retention (renal edema), lymphatic insufficiency (lymphedema) and increased capillary permeability (permeability edema). The underlying mechanism has significant impact on treatment efficacy. This review provides a comprehensive analysis of the main causative drugs by illustrating each pathophysiological mechanism and their management through an example of drug.

1. PATHOPHYSIOLOGY

Starling defined the physiologic forces involved in maintaining the fluid balance between interstitial space and plasma. They include the gradient of hydrostatic pressures, the differences in oncotic pressures, the hydraulic and oncotic permeabilities of the blood vessel wall, and the surface area available for exchange (Cho & Atwood, 2002; Michel, Woodcock, & Curry, 2020). Net pressure filtration is slightly positive for most organs and results in fluid extravasation that is balanced by its removal via lymph flow (Figure 1). Major disturbances in this balance that favors net filtration out of the vascular space (e.g., increased capillary hydrostatic pressure, decreased plasma oncotic pressure as in hypoalbuminemia) or impaired return of fluid by lymphatics from the extravascular space, will result in edema (Cho & Atwood, 2002). Local factors contribute to the maintenance of a normal capillary filtration rate. Capillary pressure regulation physiologically serves to limit profound changes in the capillary filtration rate during variations of arterial and/or venous pressures. In all tissues, an acute increase in blood pressure immediately increases the blood flow. However, in less than a minute, the blood flow returns almost at its initial level despite the blood pressure remaining high. This maintenance of a constant blood flow in spite of an increase in upstream pressure is called blood flow autoregulation (Cracowski & Roustit, 2020). Autoregulation aims at maintaining a vessel wall tension constant despite increased transmural pressure. It is a metabolic consequence of hyperoxia and of the myogenic response, the latter preventing overstretching of the blood vessels walls due to the high pressure and its subsequent interstitial edema (Scallan, Huxley, & Korthuis, 2010). Arteriolar vasoconstriction occurs in a lower limb if it is dropped to below heart level, when capillary pressure rises approximately above 25 mmHg (Cracowski & Roustit, 2020). This phenomenon, referred to as the venoarteriolar reflex, maintains capillary pressure and the transcapillary filtration rate within normal ranges, protecting capillary integrity from high hydrostatic pressures and is mostly observed in the lower limbs during venous stasis (Low, 2004).

2. DRUG-INDUCED PERIPHERAL EDEMA
Various drugs can induce or worsen peripheral edema by disrupting the delicate homeostasis between transcapillary flow, edema safety factors and lymphatic drainage capacity (Figure 2). Although most often pitting and bilateral, some drugs are involved in the development of peripheral edema that is readily erythematous (e.g., dopaminergic agonists (Wood, 2010), pemetrexed (D’Angelo, Kris, Pietanza, Rizvi, & Azzoli, 2011)) or unilateral (e.g., sirolimus (Rashid-Farokhi & Afsar, 2017)). In addition to aggressive fluid resuscitation and preparation providing a significant amount of sodium, drug-induced edema entails four mechanisms, namely precapillary arteriolar vasodilation (vasodilatory edema), sodium and water retention (renal edema), lymphatic insufficiency (lymphedema) and increased capillary permeability (permeability edema). In most situations, several mechanisms occur and contribute synergistically to edema genesis. The underlying mechanism directly affects treatment efficacy.

The aim of this review is to raise awareness on the mechanisms involved in drug-induced peripheral edema. Each of these mechanisms is illustrated through an example of the most notable drug. Drug-induced angioedema, whether mediated by bradykinin (e.g., angiotensin-converting enzyme inhibitors), histamine (e.g., beta-lactams) or leukotrienes (e.g., non-steroidal anti-inflammatory drugs), is regarded as permeability edema. However, given its predominantly non-peripheral location (e.g., facial, laryngeal or gastrointestinal involvement), it will not be discussed in this review. This review does not cover drugs that may cause edema by a primary indirect mechanism, such as heart failure (Page et al., 2016) or hypoalbuminemia as in glomerular injury (Markowitz, Bombback, & Perazella, 2015) and liver injury (European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, Clinical Practice Guideline Panel: Chair:, Panel members, & EASL Governing Board representative:, 2019).

2.1 VASODILATORY EDEMA

2.1.1 Main drugs involved

Drugs inducing preferential precapillary arteriolar vasodilatation rise capillary hydrostatic pressure, therefore increasing extravasation from the vascular space into the interstitium. The main causative medications include antihypertensive agents (e.g., calcium channel blockers, minoxidil, hydralazine (Messerli, 2002)), antiparkinsonian drugs (Borovac, 2016; Perez-Lloret et al., 2014; E. K. Tan & Ondo, 2000; E.-K. Tan, 2007; Wood, 2010) potentially through peripheral D1 receptors stimulation (Zeng, Zhang, Asico, Eisner, & Jose, 2007), antidepressant inhibiting 5-HT2 receptors (Ravi, Ravishankar, & Andrade, 2014; Tuman, Tuman, Tuman, & Tuman, 2018; Uguz, 2014), antipsychotics with α1-adrenolytic effect and/or inhibitory effect on 5-HT2 receptors (Hosseini & Ahmadi, 2012; Umar & Abdullahi, 2016), baclofen (Bence et al., 2014) potentially through GABAergic vasodilatation (Estato, Araujo, Bousquet, & Tibiriçä, 2004; Zhang & Mifflin, 2010), endothelin receptors antagonists (Wei et al., 2016), insulin (Lalonde & Romero, 2019)).

2.1.2 Calcium channel blockers

A classical pharmacodynamic effect of calcium channel blockers is to induce diffuse and bilateral swelling of the feet, ankles, and sometimes lower legs that worsen throughout the day and improve overnight (Sica, 2003). This effect is a local effect and not the consequence of water and/or sodium retention (van Hamersvelt, Kloke, de Jong, Koene, & Huysmans, 1996). While calcium channel blockers increase the subcutaneous tissue pressure (Messing, Van Essen, Smith, Smits, & Stuyker-Boudier, 1991), the prevalence of peripheral edema is lower with lipophilic dihydropyridines (DHPs) such as manidipine or lercanidipine (de la Sierra, 2009; Makani, Bangalore, Romero, Htyte, et al., 2011; Messerli, 2002). The mechanism explaining this effect is more complex than routinely described. First, calcium channel blockers vasodilate arterioles but not venules (Messing et al., 1991). This selective arteriolar vasodilatation is often described as the main cause for the increased capillary pressure observed under calcium channel blockers. However, this cannot account for the whole effect, as venules are capacitance vessels exerting only a weak resistance to the blood flow. The second mechanism linked to the voltage operated channel blockade itself is the alteration of blood flow autoregulation (Gustafsson, Lämme, Bjerkhoel, Johansson, & Lundvall, 1989) in addition to the abolition of the spontaneous vasomotion. Indeed, the target of calcium channels blockers, the channel pore of Cav1.2 subtype, is involved in the myogenic response (Retailleau et al., 2016; Tykocki, Boerman, & Jackson, 2017). The third mechanism
is the alteration of the venoarteriolar reflex, as calcium channel blockers inhibit postural skin vasoconstriction at the dorsum of the foot (Iabichella, Dell’Omo, Melillo, & Pedrinelli, 1997; Pedrinelli, Dell’Omo, & Mariani, 2001) explaining the upright posture prominence and further compounds the problem.

Vasodilatory edema occurs in 12 to 16% of patients on DHP (Makani, Bangalore, Romero, Htyte, et al., 2011; Vukadinović et al., 2019). It is dose-dependent (Makani, Bangalore, Romero, Htyte, et al., 2011; Messerli, 2002), and varies according to the time of intake (lower frequency with bedtime ingestion (Hermida, Ayala, Mojón, & Fernández, 2008)) and age (Messerli, 2002). Age is an important determinant insofar as tissue wasting reduces interstitial hydrostatic pressure, acting as the main counterforce in hydrostatic-driven edema (Sica, 2003), in addition to functional venous insufficiency due to valve dysfunction. It may become more severe during long-term therapy (Makani, Bangalore, Romero, Htyte, et al., 2011; Messerli, 2002). Faced with these edema, many pharmacoepidemiologic studies have shown that a very frequent therapeutic re-
flex consists in initiating diuretics (Savage et al., 2020; Vouri et al., 2019). Indeed, 2.3% of patients over 65 years of age newly treated with DHP experience this prescription cascade within one year of initiation (Vouri et al., 2019). Compared to renin angiotensin aldosterone system (RAAS) inhibitor prescription, this risk is significantly increased by 2.4 after a 3-month treatment (Savage et al., 2020). Unfortunately, given that calcium channel blockers are intrinsically natriuretic and DHP-induced edema results from preferential arteriolar vasodilatation combined with autoregulation disruption; DHP-related edema has no relationship with sodium and/or water overload and is therefore diuretic-resistant (Messerli, 2002). A greater reduction of vasodilatory edema is achieved with the addition of a RAAS inhibitor to DHP, strategy that significantly reduces the risk of withdrawal due to peripheral edema by 62% (relative risk 0.38; 95% confidence interval, 0.22-0.66) (Makani, Bangalore, Romero, Wever-Pinzon, & Messerli, 2011). This elegant pathophysiologic observation is explained by the ability of RAAS inhibitors to decrease postcapillary resistance (i.e., venous dilatation), thus normalizing hydrostatic pressure within the capillary bed, thereby reducing fluid extravasa-
tion (de la Sierra, 2009; Makani, Bangalore, Romero, Wever-Pinzon, et al., 2011). Depending on the clinical context, several strategies may be considered as dosage reduction, DHP cessation, switch to another DHP or combination therapy with a RAAS inhibitor (de la Sierra, 2009; Makani, Bangalore, Romero, Wever-Pinzon, et al., 2011). Traditional measures such as limiting the amount of time that a patient is upright and/or considering the use of graduated compression stockings are useful adjunctive therapies (Sica, 2003). Furthermore, experimental data have shown off-target inhibitory effect of gabapentinoids (i.e., gabapentin, pregabalin) on the Cav1.2 channel pore of arterial myocytes (Bannister et al., 2009, 2012; Behuliak et al., 2018), sugges-
ting that gabapentinoid-related edema (Freynhagen et al., 2015; Wiffen et al., 2017) may exhibit the same characteristics as induced by cardiovascular calcium channel blockers.

2.2 RENAL EDEMA

2.2.1 Main drugs involved

Drugs causing fluid overload increase capillary hydrostatic pressure which is transmitted to the capillary bed, predisposing to edema formation. Several drugs induce salt and/or water retention either directly by antinatriuretic and/or antiaquaretic action (e.g., androgens (Basaria et al., 2010; Beck, Thompson, & Oder-
matt, 2020; Quinkler et al., 2005), aromatase inhibitors (Robert & Denduluri, 2018; G. Walker, Xenophontos, Chen, & Cheung, 2013), estrogens (Stachenfeld, 2008), gonadotropin releasing hormone analogues (Robert & Denduluri, 2018), growth hormone (Hazem et al., 2012; Kamenicky et al., 2008), corticosteroids (Beck et al., 2020), endothelin receptor antagonists (Wei et al., 2016), opioids (Gardner-Nix, 2002; I. Mahé, Chassany, Grenard, Caulin, & Bergmann, 2004; Veizi, Tornero-Bold, & Hayek, 2016; Yeo, Koh, & Lim, 2016)) or indirectly by reactive stimulation of RAAS (e.g., α1-adrenergic blockers (Sica, 2005), diazoxide (Komatsu et al., 2016; van Hamersvelt et al., 1996)) or by increase sodium tubular reabsorption in case of renal hypoperfusion (e.g., minoxidil, hydralazine (Sica, 2003)).

2.2.2 Non-steroidal anti-inflammatory drugs

Peripheral edema is not uncommon as it occurs in 2–5% of non-steroidal anti-inflammatory drugs (NSAIDs) users (C. Walker & Biasucci, 2018), especially when patients are at risk of increasing susceptibility to
clinical effect of NSAID-induced vasoconstriction (e.g., absolute volume depletion, old age) (Whelton, 1995, 2000). NSAID-induced peripheral edema has both direct and indirect mechanisms that are independent to RAAS; they otherwise inhibit (Beck et al., 2020; Cabassi et al., 2020; Frishman, 2002). Disruption of renal homeostasis induced by the inhibition of cyclooxygenase (COX)-dependent generation of prostaglandins (PG) is the primary mechanism. The COX isoforms (i.e., COX-1 and COX-2) are expressed at different levels by each nephron component. They synthesize several PG (Cabassi et al., 2020) including PGE$_2$ and PGI$_2$ which are both involved in NSAID-associated peripheral edema. Firstly, NSAID-induced PGE$_2$ lowering decrease both natriuresis in the thick ascending loop of Henle (Frishman, 2002) and aquaresis through facilitation of arginine vasopressin activity in the collecting duct (Cabassi et al., 2020). Secondly, NSAIDs inhibit PGI$_2$-related afferent arteriole vasodilatation, reducing glomerular filtration rate and thus promote proximal tubular reabsorption (Frishman, 2002). Nonselective and COX-2 selective NSAIDs have similar incidence of peripheral edema (Cabassi et al., 2020; C. Walker & Biasucci, 2018), supporting that fluid retention is mostly COX-2 mediated (Cabassi et al., 2020; Frishman, 2002). Edema, which is usually mild and subclinical (typical weight gain 1 to 2 kg), exhibits early onset such as within the first week of NSAID use, and is reversible on discontinuation of the drug (Whelton, 2000).

2.3 LYMPHEDEMA

2.3.1 Main drugs involved

The pathophysiological mechanism of drug-induced lymphedema results from impaired lymphatic drainage that overcomes transcapillary filtration. Few drugs are involved such as tamoxifen (Das et al., 2015), taxanes (e.g., paclitaxel (Zamora et al., 2019) and docetaxel (Park et al., 2014)), mTOR (mammalian target of rapamycin) inhibitors (e.g., everolimus, sirolimus (Gharbi, Gueutin, & Izzedine, 2014)) and PI3K/AKT inhibitors (Daniell et al., 2019) (e.g., alpelisib, idelalisib). Peripheral edema is a common adverse reaction to tamoxifen that is associated with a substantial risk of drug withdrawal (Cluze et al., 2012). Several studies have found, after adjusting for age, stage, breast cancer treatment, and axillary lymph node dissection, a trend towards a positive association of tamoxifen use and lymphedema (Das et al., 2015). These observations are supported by experimental data where Morfoisse et al. (Morfoisse et al., 2018) found that tamoxifen, by blocking estrogen receptor-α, interferes with lymphatic vasculature stability, predisposing to lymphedema aggravation. Apart from tamoxifen, all these drugs interfere with the vascular endothelial growth factors (VEGF) involved in lymphangiogenesis, namely VEGF-C which selectively activates VEGFR-3 through the PI3K/AKT pathway (Huber et al., 2007; Wang, Xu, Wen, Wang, & Yuan, 2019; Zamora et al., 2019). Diagnosis is made difficult by the fact that these drugs are also responsible for peripheral edema due to increased capillary permeability (e.g., taxanes (Sibaud et al., 2016), sirolimus (Zaza et al., 2013)) and that early-stage lymphedema mimics other causes of extremity swelling (Grada & Phillips, 2017). As in other causes of lymphedema (Grada & Phillips, 2017), transient nontender pitting edema occurs in newly developed drug-induced lymphedema. Over time, the skin becomes indurated with a leathery texture because of skin thickening and fibrosis.

2.3.2 mTOR inhibitors

Regarding mTOR inhibitors-related edema, incidence is higher in kidney than in liver transplant recipients and approximately 5-fold higher with sirolimus compared to matched everolimus-treated patients (Gharbi et al., 2014). Sirolimus (Huber et al., 2007; Wang et al., 2019) directly impairs lymphatic drainage through VEGF-C/VEGFR-3 signaling, leading to stasis of extravasated tissue fluid and macromolecules (Gharbi et al., 2014). To such an extent that sirolimus is used to treat lymphatic malformations related to PI3K/AKT/mTOR upregulation (Fereydooni, Dardik, & Nassiri, 2019). In a review of 26 cases, the time from sirolimus initiation to lymphedema onset ranged from 1 to 30 months (Rashid-Farokhi & Afshar, 2017). Sirolimus-induced lymphedema is usually unilateral or asymmetrical especially when located in upper extremities (Rashid-Farokhi & Afshar, 2017). Diuretics are ineffective and it may progress to permanent scleroderma-like lesions (E. Mahé et al., 2005) when the dosage is not reduced or drug is not interrupted early (Gharbi et al., 2014). In most patients with mTOR inhibitor-related lymphedema, early withdrawal of the medication leads to partial or complete resolution of edema after several months (Rashid-Farokhi & Afshar, 2017).
Afshar, 2017).

2.4 PERMEABILITY EDEMA

2.4.1 Main drugs involved

Drugs that can increase capillary permeability to proteins lead to the loss of protein-rich fluid from the intravascular to the interstitial space. The main drugs causing permeability edema include anticancer drugs (Azzoli et al., 2003; D’Angelo et al., 2011; Giles, O’Dwyer, & Swords, 2009; Hack, Bruyé, & Koepfen, 2014; Izzedine, El-Fekih, & Perazella, 2016; Mertz, Lebrun-Vignes, Salem, & Arnaud, 2019; Rizzo, Aman, van Nieuw Amerongen, & Dudek, 2015; Sibaud et al., 2016; Siddall, Khatri, & Radhakrishnan, 2017), cytokines (Mertz et al., 2019), ambrisentan (Vercauteren et al., 2017) and calcineurin inhibitors (Mertz et al., 2019) (Figure 2). This mechanism of edema is becoming an increasingly common clinical picture with the advent of multikinase inhibitors that interfere with the signaling pathways involved in endothelial permeability (e.g., BCR-Abl inhibitors (García-Gutiérrez & Hernández-Boluda, 2019), ALK inhibitors (Hack et al., 2014; Izzedine et al., 2016)). Capillary leak syndrome (CLS) represents the paroxysmal picture of permeability edema. As in idiopathic CLS (i.e., Clarkson disease) (Druey & Parikh, 2017), drug-induced CLS is characterized by fluid-refractory hypotension, pathognomonic profile of hemoconcentration with rising hematocrit and paradoxical hypoalbuminemia in the absence of secondary causes for such abnormalities, and systemic pitting edema (Siddall et al., 2017). Cytokines (e.g., interleukin-2, granulocyte colony stimulating factor), and antineoplastic agents, especially gemcitabine and clofarabine, are the main drugs involved in secondary CLS (Jeong et al., 2019; Mertz et al., 2019).

2.4.2 BCR-Abl inhibitors

All BCR-Abl (breakpoint cluster region and Abelson) inhibitors are associated with peripheral edema (García-Gutiérrez & Hernández-Boluda, 2019) and serous effusions (García-Gutiérrez & Hernández-Boluda, 2019; Rizzo et al., 2015). The risk of peripheral edema is greater with imatinib and dasatinib both in terms of incidence (e.g., periorbital and/or extremity edema in 74-84% imatinib-treated patients (Kim et al., 2015)) and in terms of severity where they are grade 3/4 in 5-10% of patients (García-Gutiérrez & Hernández-Boluda, 2019). The precise molecular substrate remains elusive but could be related to both on-target effects on endothelial Abl kinases (affecting vascular permeability and cell-cell junction dynamics) (Rizzo et al., 2015) and off-target inhibitory effects (e.g., Src kinases, platelet-derived growth factor receptors) (Giles et al., 2009). Both Src kinases and platelet-derived growth factor receptors regulate vascular permeability; the latter also affecting interstitial hydrostatic pressure (Giles et al., 2009). Imatinib has been shown to induce CLS (Hinchcliff, Lomasney, Johnson, & Varga, 2016; Jeong et al., 2019). Pathophysiology involves a decrease in the oncotic reflection coefficient through the capillary wall. It is thought to be due to an endothelial dysfunktion and weakening of endothelial cell-to-cell binding secondary to hypercytokinemia, resulting in rapid extravasation of albumin into the extravascular space (Druey & Parikh, 2017; Siddall et al., 2017). Because of its uncertain pathogenesis, the management of drug-induced CLS remains largely empiric and mainly based on drug discontinuation and corticosteroids therapy to reduce cytokine release (Siddall et al., 2017). Surprisingly, recent data suggest a potential benefit of imatinib in certain forms of capillary hyperpermeability syndromes, including Clarkson disease (Rizzo et al., 2015).

3. CONCLUSION

Many drugs are accountable, through different mechanisms, for peripheral edema. Severity is distinctly variable ranging from slight edema of the lower limbs to anasarca pictures as in capillary leak syndrome. Although most often pitting and bilateral, some drugs are associated with peripheral edema that is readily erythematosus (e.g., dopaminergic agonists, pemetrexed) or unilateral (e.g., sirolimus). Apart from calcium channel blockers, drug-induced peripheral edema is underrecognized and misdiagnosed, frequently leading to a prescribing cascade. Four main mechanisms are involved, namely precapillary arteriolar vasodilation (vasodilatory edema), sodium/water retention (renal edema), lymphatic insufficiency (lymphedema) and increased capillary permeability (permeability edema).
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ANNEXES

Figure 1 – Physiology of capillary fluid exchange. Capillary hydrostatic pressure decreases along the capillary path and becomes lower than oncotic capillary pressure, ... in interstitial space which is balanced by removal of interstitial fluid via the lymphatics according to its flow rate (Q λ) which finally returns to the bloodstream through the thoracic duct.

Figure 2 – Main pathogenic mechanisms and causative drugs involved in peripheral edema. The four main mechanisms are illustrated: lymphedema (impaired lymphatic drainage), cardiac failure (increased capillary hydrostatic pressure), kidney disease (increased capillary oncotic pressure), and liver disease (increased capillary oncotic pressure).

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