Review

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Clarxon Disease
(Capillary leak syndrome)

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مرض كلاركسون (متلازمة التسرب الشعيري)

مها خلف علي ، فاطمة قاسم محمد

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ABSTRACT

Capillary leak syndrome (CLS) is a challenging and even fatal disorder that is becoming more widely known (CLS). After the initial hazy symptoms, the interesting The dual paradox of broad severe edema & hypovolemia, as well as hemoconcentration and hypoalbuminemia, which is a characteristic of CLS, manifests. . A poor outcome during The iatrogenic fluid surplus during the leak phase is often linked to the spontaneous resolutive phase. The main causes of CLS are malignancy, viruses, inflammatory diseases, medications (anti-tumoral therapy), and malignancy. In honor of its discoverer, the idiopathic variety is known as Clarkson's disease. A substantial, transient, and complex endothelium disruption, the mechanisms of which are now unclear, is a component of CLS' pathogenesis. Empirical and experience-based therapy consists of pharmacological treatment during the acute stage (perhaps with the addition of medication) that increase rates of cyclic adenosine monophosphate (cAMP) in the most severe patients), for avoiding relapses with monthly administration of adaptable immunoglobulins. Due to the scattered nature of the CLS literature, we set out to gather and summarize the most recent studies on the condition in order to help in its identification, comprehension, and treatment.

Keyword: Antineoplastic agents, monoclonal antibodies, cardiovascular system.

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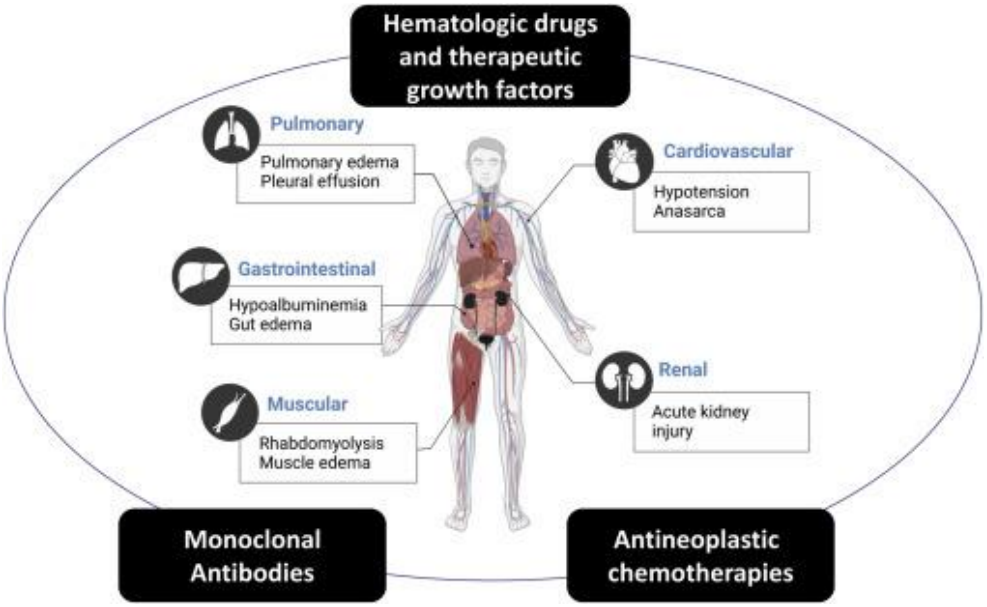
1.INTRODUCTION

The vascular syndrome of leaks (VLS) and crisis of leakage symptoms (CLS) were first recognized 1960, via Clarkson [1] . The second recognized Epilepsies systemic capillaries flow syndrome is a condition,which affected Clarkson (ISCLS). The distinguishing characteristic of this entity is the simultaneous medical and biological conflict (during leak phase) that connects hemoconcentration and hypoalbuminemia and Hypoperfusion shock or widespread pits edema with hypovolemia [2], [3]. Afterward, secondary kinds of CLS were discovered, especially following the creation of immunotherapies and anti-tumor medications. CLS has an undetermined prevalence and a high death rate due to misdiagnosis and ambiguous symptoms [4] ,[5]. These data (incidence, risk factors, and mortality on cancer patients) were the subject of recent oncologic meta-analyses [6], [7]. The lack of pathophysiology understanding at the moment may be explained congenital form's uncommon and the new discovery of subsequent CLS [8]. Recent oncologic meta-analyses [6], [7] examined the information on cancer incidence, risk factors, and patient mortality. The idiopathic form's rarity and the recent discovery of secondary CLS, [8] may both contribute to the current lack of pathophysiology understanding. Significant arterial leakage resulting from transient endothelial dysfunction and hyperpermeability was identified in recent studies. Even despite using precautionary The five-year mortality rate was reduced dramatically by intravenous immunoglobulins from 80 - 15%. and boosted ten-year mortality from 32% into 94% [8],[9]Acute variants of CLS still have a 20–30% mortality rate [2] , [8] , which is substantial.Although interest in CLS has grown over the past ten years, it is still a diagnostic niche. In light of the high mortality, a lot of false diagnoses, unknown cause, and challenging treatment for severe situations, we set out to synthesize and combine the most recent the ability to use primary and secondary CLS.



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the cardiovascular system, kidneys, lungs, gastrointestinal system, and muscles systems are among the organ systems that are impacted by capillary leak syndrome. Anticancer medication courses connected to syndrome of capillary leaks are represented by the boxes in black.

Section snippets

a condition with three stages:

A tripartite pattern is commonly followed by a severe CLS relapse. [10],[11]. Onset stage (inconstant) consists of the worsening of general health (common cold symptoms such as body aches, weariness, weakness, disorientation, and nausea), chills, and digestion (stomach pain, vomit, and dysentery) issues (myalgia, cough, rhinorrhea). The change to the leak stage is abrupt and could be lethal, despite the fact that the early expression is typically faint and deceptive. [10].

The subsequent leak

diseases and disorders connected to cls

In the literature, there is a lot of ambiguity surrounding the prognosis of CLS. In reality, CLS is usually compared as for SIRS, a greater Inflammatory responses reaction disorder) is a common disorder.). Some of the well-known etiologies that might result in SIRS are intense pancreatic [11], hemophagocytic lymphohistiocytosis, and blood poisoning shock [10], major injury, cardiothoracic surgery, cytokine release crisis (CRS), etc.[12].

2. BLOOD CAPILLARIES HEMORRHAGE SYNDROME CAUSED BY DRUGS

Varieties of medications were associated to disorder of capillary leakage IL-2 is a cytokine., which is used to treat cancer, oedema, breathlessness, fever, chills, nauseousness, vomited, and diarrhea have all been linked to it [13].

Animal studies using IL-2 increased the albumin-induced vasculature penetration [14].

Additionally, the interleukin IL-11 and IL-12 were connected to disorder of capillaries leaking Gemcitabine therapy for cancer has been associated with AKI, noncardiogenic pulmonary edema, hypotension, and systemic edema ([15].

Studies on lung cancer patients treated with gemcitabine revealed a substantial increase in IL-2 & TNF- as a result of treatment [16]. Monoclonal antibodies have the power to abruptly activate enormous numbers of immune cells, which has the ability to increase several cytokines [9].

hrs. until minutes following the administration of the a single-chain antibody, the symptoms of this particular capillary leak syndrome, also known as cytokine release syndrome, start to show. OKT3, an antibody response stops T cells' CD3 from functioning. OKT3 side effects include Flu-like symptoms, chills, coughing, confusion, vomiting, hypertension, with tachycardia [17]. Increases in TNF-, IL-2, and interferon are linked to the OKT3 initial dosage response [18] More drastic responses have all

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been connected to higher serum TNF- increases [19]. Rituximab and alemtuzumab, two monoclonal antibodies,which are used to treat hematologic malignancies, have a side effect known as the cytokine release syndrome. In contrast to rituximab, which the past demonstrated to elevate TNF-, interferon-, and IL-6 related with In individuals with B-cell leukemia, alemtuzumab was already proven to improve blood leak disorder. TGN1412, a presence of anti antibody, has been studied. may be the greatest illustration of a stimulant severe capillary collapse with significant organ dysfunction. Six healthy volunteers received TGN1412, and all patients had acute renal damage with metabolic acidosis, respiratory infiltrates on both sides, diffuse intravascular coagulation, hypotension, and the need for continuing renal replacement therapy were all present. Numerous cytokines have increased significantly in all cases. The IL-6 and IL-4 levels were significantly elevated in the two patients with the most severe disease. Steroids have been successful in reducing the signs and indicators of drug-induced capillaries leak crisis [20].

3. PATHOPHYSIOLOGY

The fundamental pathophysiologic problem that underlies all disorders that result in capillary leak syndrome is an increase in capillary permeability to proteins. [21]. As a result, fluid rich in proteins is lost from the intravascular to the interstitial region. It is believed that Capillary leak always has hypercytokinemia as its underlying cause. Theoretically, molecules in the plasma with a minimum molecular weight of 200 kDa and a maximum molecular weight of 900 kDa were released into the interstitial space [22], who evaluated a patient with SCLS. (For reference, the molecular weight of albumin is 66.5 kDa.) Atkinson et alstudy's , showed that within the first 12 hours of the capillary's existence, there was a 30% to 50% loss of albumin from the intravascular region leak phase. The strength of the connections between nearby endothelial cells determines the endothelium's capacity to act as a barrier between intravascular and interstitial location.. Tight junctions and adherens junctions (AJs), two separate forms of cell junctions, are used by endothelial cells to join to neighboring cells [23]. AJs seem to be the most significant part of endothelial cell-to-cell communication and, consequently, permeability, next to the brain. [24] A crucial element of the AJ is vascular endothelial cadherin. [23] . Mice with vascular endothelial cadherin-blocking antibodies show increased vascular permeability in the heart and lungs. [20]. The AJ is weakened and permeability is increased while the integrity of the endothelial architecture is maintained by mild inflammatory stressors that result in vascular endothelial cadherin internalization. [25] Inflammatory stimuli that are more potent cause endothelial cells to split, leaving spaces between them and much increased levels of permeability. [19]It has been established that sepsis and certain cytokines alter the AJ, increasing vascular permeability [23]. After being exposed to the acute onset serum from SCLS patients, human microvascular endothelial cells underwent changes in microvascular permeability, AJ integrity, and vascular endothelial cadherin localisation at the AJ. [26] Quiescent serum incubation had no effect on human microvascular

endothelial cells. According to the authors, a soluble component in the plasma is what causes an increase in endothelial permeability during the capillary leak phase. Despite the fact that endothelial cell connections have not changed in relation to additional capillary leak syndrome causes. Their similar clinical phenomenology suggests that the illnesses have a common molecular origin.

4. hemodynamic manifestations

The loss of protein-rich fluid from the intravascular space results in the release of vasopressin, activation of the sympathetic nervous system, and subsequent renin, angiotensin, and aldosterone system activation [27] . Systemic edema and exudative serous cavity effusions are the results of the salt and water retention that follows. [24]. When a capillary leak develops quickly and severely, Significant hemoconcentration can happen in conditions including SCLS, viral hemorrhagic fever, OHSS, and ricin poisoning. [25]. It is possible to determine the severity of a capillary leak using this hemoconcentration. In disorders with a late start or hematologic involvement, hemoconcentration is not observed. In the most severe situations, hypovolemic shock can result from any cause of capillary leak syndrome, including SCLS, HLH, [28], OHSS, differentiation syndrome [27], ricin, engraftment syndrome, and hemorrhagic fever , and others. OCT3, gemcitabine, IL-2, rituximab, anti-CD28 antibody [1].

5. PULMONARY MANIFESTATIONS

It has been shown that pleural effusions, which are exudative in nature result from every known etiology that causes capillaries leak syndrome [24] When capillary leak syndrome is severe, noncardiogenic pulmonary edema is also present.. When capillary permeability returns to normal during SCLS, The interstitial fluid that has collected is forced back into the intravascular region. After their blood pressure has stabilized, patients who received significant amounts of intravenous fluids during resuscitation may develop life-threatening pulmonary edema [25]. Additionally connected to hemorrhagic fevers is After intravenous fluid resuscitation, pulmonary edema that is not cardiac in origin . Noncardiogenic pulmonary edema can develop quickly after receiving a significant fluid infusion or early in the course of a number of diseases.. Additional pulmonary symptoms include acute respiratory distress syndrome, differentiation syndrome, pulmonary hemorrhage in Drug-induced capillary leak syndrome, HLH, OHSS, engraftment syndrome,[29]. Dyspnea and mild hypoxia are the most common respiratory abnormalities detected in OHSS, despite the presence of noncardiogenic pulmonary edema and pleural effusions, since Diaphragmatic descent is hampered by large-volume ascites. This results in low lung capacities and an increase in breathing work [30].

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6. RENAL MANIFESTATIONS

The typical symptom of capillary leak syndrome is AKI.. ATN and prerenal induce intravascular volume depletion, which is the most common cause of AKI [31]. Animal models of Numerous illnesses imply that cytokines may be involved in renal tubular damage. As a result, cytokines may also contribute to hypotension in the progression of capillary leak syndrome in ATN. Rhabdomyolysis's onset and the subsequent myoglobinuria help certain cases of SCLS lead to the development of ATN. In addition to myoglobinuria and Infrequently, intravascular hemolysis with hemoglobinuria and cortical necrosis causes AKI in victims of snakebite envenomation.A small percentage of patients with HLH develop glomerular lesions connected to the nephrotic syndrome [32], Other systems), although early in the course of their condition, an active urine sediment may briefly emerge in individuals with VHF and ricin poisoning, suggesting a prerenal and acute tubular necrosis with minimal glomerular dysfunction. abdominal compartment syndrome brought on by restricted ascites, It could happen in OHSS and cause AKI in addition to intravascular volume loss [33].

Since edema develops all across the body, it is anticipated that edema buildup will affect most systems. However, there aren't enough detailed data sets on how capillary leak syndrome affects other organ systems. Muscular edema and rhabdomyolysis can cause compartment syndrome in SCLS patients. People with capillary leak frequently experience abdominal pain, nauseousness, and vomiting. abdominal discomfort in capillary leak syndrome may be mediated by gastrointestinal tract edema, according to the fact that it can get worse with increased fluid resuscitation confirmation of intestinal edema in a case of SCLS with hemorrhagic fever in individuals with SCLS [34]

7.DIFFERENTIAL DIAGNOSIS

Sepsis and septic shock typically share symptoms with Capillary leak syndrome ranges from mild to severe. Therefore, empirical antibiotic therapy is typically advised for patients who are Possibly suffering from capillary leak syndrome [28], and the possibility of anaphylactic shock, another possible diagnosis for Rapid hemodynamic collapse should be taken into account while determining SCLS's differential diagnosis..[35] Additionally, Gleich syndrome, Both acquired and inherited angioedema (C1 inhibitor deficiency) can all be misdiagnosed for Capillary leak condition (eosinophilic angioedema). Skin, upper airway, and digestive tract edema can all be signs of these illnesses. [34].

8.Conclusion

Due to a lack of specific diagnostic criteria, CLS is a rare and possibly lethal illness that is underdiagnosed. The most accurate CLS feature would be the dual clinico-biological paradox that links hemoconcentration and hypoalbuminemia as well as significant hypovolemia and extensive edema. According to studies on the biology of

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acute endothelial dysfunction, soluble factors interact with subsequent inflammatory pathways. CLS frequently has a circulation tied to it.

Conflict of interests.

There are non-conflicts of interest.

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الخلاصة

مرض كلاركسون او متلازمة التسرب الشعيري (capillary leak syndrome) اضطرابا صعبا وحتى مميتا يتمثل بخروج البلازما من جهاز الدوران عبر جدران الشعيرات الدموية الى الحيزات العضلية, الانسجة المحيطةّ, والأعضاء وتجاويف الجسم وتكون اكثر شيوعا في حالة الانتانات واقلها في امراض المناعة الذاتية ومتلازمة فرط التنبيه المبيضي, والتسمم بلدغة الافعى والريسين. كما ان بعض الادوية يمكن ان تسبب تسربا شعريا (وتعد مصدرا ثانويا لذلك) بما في ذلك ادوية العلاج الكيمياوي, والاضداد وحيدة النسيلة وبعض الانترلوكينات.

فمرض كلاركسون هو حالة طبية نادرة, يمتاز بنوبات عكسية التي من خلالها تنفصل خلالها الخلايا المبطنة للشعيرات الدموية لمدة (يوم – ثلاثة) أيام، لأن كل نوبة قد تسبب تلفًا في عضلات الأطراف وأعصابها، وكذلك في الأعضاء الحيوية بسبب التسرب المحدود فمتلازمة التسرب الشعيري الجهازي بالتالي مرض يهدد الأطراف والحياة،. فهي غالبًا ما تُشخص على أنها متلازمة فرط اللزوجة، أو إنتان كثرة ,كريات الدم الحمر، أو كثرة الحمر الحقيقية،

لا تحدث عادةً في البطن والجهاز العصبي المركزي والأعضاء (بما في ذلك الرئتين), ولكن يكون التسرب في الأطراف بكثافة كافية لحدوث صدمة دورانية ومتلازمات الحيز، مع انخفاض ضغط الدم بشكل كبير، تركّز الدم (زيادة كثافة الدم) ونقص ألبومين الدم (هو بروتين رئيسي) لوجود أسباب أخرى غير مفهومة تسبب هذه الأعراض, فقد تم اعداد هذه المقالة من اجل المساعدة في تحديد وفهم علاج المرض.

الكلمات المفتاحية: الاضداد وحيدة النسيلة ,الجهاز الوعائي, العوامل المضادة للسرطنة.