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LESER-TRELAT SIGN AND ITS MAIN FEATURES: A SYSTEMATIC LITERATURE REVIEW

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Abstract: Leser-Trélat sign (TLS) is a rare paraneoplastic syndrome characterized by the sudden onset of multiple seborrheic keratoses (QS), indicating an underlying malignancy. The cancers most associated with TLS occur in the gastrointestinal tract and, as they are more common in elderly people, some authors question its legitimacy as a predictor of malignancy. So, this study aimed to compile all case reports published in the last ten years, to analyze their common characteristics, such as the sex and age of the people affected, as well as the main associated malignancies, the evolution of skin lesions and its relationship with the onset of cancer. A bibliographic search was carried out in the databases: *Medical Literature Analysis and Retrieval System Online* (Medline) via PubMed, *Scientific Electronic Library Online* (SciELO) and Latin American and Caribbean Literature in Health Sciences (LILACS), using the term: *Leser-Trelat*. Based on the selection criteria, 13 articles were included in this study and it was found that the disease is more common in the elderly, with no sex predilection. The most common location of QS was on the back and chest, with sudden onset and with a higher occurrence of gastric and hepatocellular adenocarcinoma, in addition to cutaneous T lymphoma. Despite the need for more studies to improve the understanding of the disease, it is concluded that TLS must indeed be considered a paraneoplastic syndrome and, therefore, an omen for screening for hidden malignancies.
Keywords: Leser-Trélat, Cancer, Seborrheic Keratosis.

INTRODUCTION

Leser-Trélat sign (TLS) is a rare paraneoplastic syndrome characterized by the sudden eruption of multiple seborrheic keratoses (QS) in patients with underlying malignancy [1-13] hidden or known [14]. These benign skin lesions rapidly increase in number and size over a period of weeks to months.[10,14] and may precede, follow or occur concurrently with a malignancy [3,14].

Lesions may present as macules, plaques and papules, with a verrucous appearance, with a color that varies from brown to black, with a waxy surface. [15]. Os cânceres mais associados ao SLT ocorrem no trato gastrointestinal[2,3,5,12,15-17] and its pathogenesis is not very well understood [12,18,19]. However, it is believed that the multiple QS are the result of an exacerbated cell proliferation of keratinocytes stimulated by growth factors produced by the tumors themselves [11,15,20,21]. And, as they are more common in older people, some authors question their legitimacy as a predictor of malignancy [13,18,22,23].

From the scarcity of systematic reviews on SLT in the scientific literature; Despite the controversy on the subject and its importance for the diagnosis of some occult malignancies, this study aimed to compile all case reports published in the last ten years, to analyze their common characteristics, such as gender, age and malignancies. associates; as well as the evolution of skin lesions and their relationship with the onset of cancer.

METHODS

SEARCH PROTOCOL AND STRATEGY

This systematic review followed the recommendations of the *Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA). The bibliographic search was carried out from January to October 2021, in the following databases: *Medical Literature Analysis and Retrieval System Online* (Medline) via PubMed, *Scientific Electronic Library Online* (SciELO) and Latin American and Caribbean Literature in Health Sciences (LILACS), using the term *Leser-Trelat*.

SELECTION OF STUDIES AND DATA EXTRACTION

As inclusion criteria, the original journals of clinical case reports involving the SLT, published in the last ten years in English, Portuguese and Spanish, were considered. Articles that did not meet these criteria were excluded from the analysis.

Then, two reviewers, blindly and independently, performed the eligibility and inclusion of the studies in two stages: screening of titles and abstracts and full reading. In the first stage, all titles and abstracts found were evaluated, based on predefined eligibility criteria for identifying relevant studies. If at least one of the evaluators included a study during this step, it was included in the subsequent step.

With the selected articles in hand, the complete reading of the texts was carried out independently, based on the eligibility criteria. The studies included were evaluated by the two previously trained reviewers, and the data were extracted into a Microsoft Excel spreadsheet, as shown in Tables 1 and 2.

RESULTS

Based on the descriptor, the search in the selected databases led to the identification of 220 potential articles for inclusion in the systematic review, 202 from Medline, 13 from LILACS and 05 from SciELO (Figure 1).

Thus, after inserting the filters, 30 articles were selected for the reading of titles and abstracts, of which 02 were excluded for being duplicates and 01 for not being a clinical case report. The remaining 27 articles were read in full, of which 01 of these was excluded for not having a diagnosis of malignancy, 04 for being a letter to the editor and 09 for not being articles of complete clinical cases, both with scarce information. Therefore, 13 articles were included in the systematic review (Figure 01).

The 13 selected articles were published between the years 2012 to 2020. Most journals reported a single clinical case, with the exception of the Jepsen et al[11] which describes two cases, a man and a woman.

So, from a total of 14 patients, SLT involvement was observed in both sexes, seven men (50%) and seven women (50%), with a mean age of 65 years, ranging from a minimum of 20 to a maximum 84 years old. The race of patients was not described (Table 01).

The most frequent location of QS injuries was in the chest and back regions, and they can also appear in the limbs, head, abdomen and neck. In all cases, there were reports that the skin lesions originated and/or increased suddenly, however, only half of the cases underwent a biopsy to confirm the diagnosis. Only 5 (35%) articles describe the evolution of QS after cancer treatment, two of which 3 (60%) observed regression of lesions (Table 01).

The malignancies most related to TLS were gastric adenocarcinoma (14.3%), hepatocellular adenocarcinoma (14.3%) and cutaneous T lymphoma (14.3%), in addition to others such as breast cancer, malignant mesothelioma, carcinoma of the skin. fallopian tube, endometrioid adenocarcinoma, renal carcinoma, leiomyosarcoma, pulmonary adenocarcinoma and leukemia (Table 01).

As shown in Table 2, of the 14 clinical cases reported, 6 (42.8%) progressed with pruritus in the region of the lesions and 4 (28.5%) reported the appearance of acanthosis nigricans (AN) together with TLS.

Despite the need for more studies to improve the understanding of the TLS, most articles (35.7%) state that the sign must indeed be considered for carrying out research on the presence of possible occult cancers and/or suggest a direct relationship of lesions with the diagnosis of cancer obtained in the reports (50%).

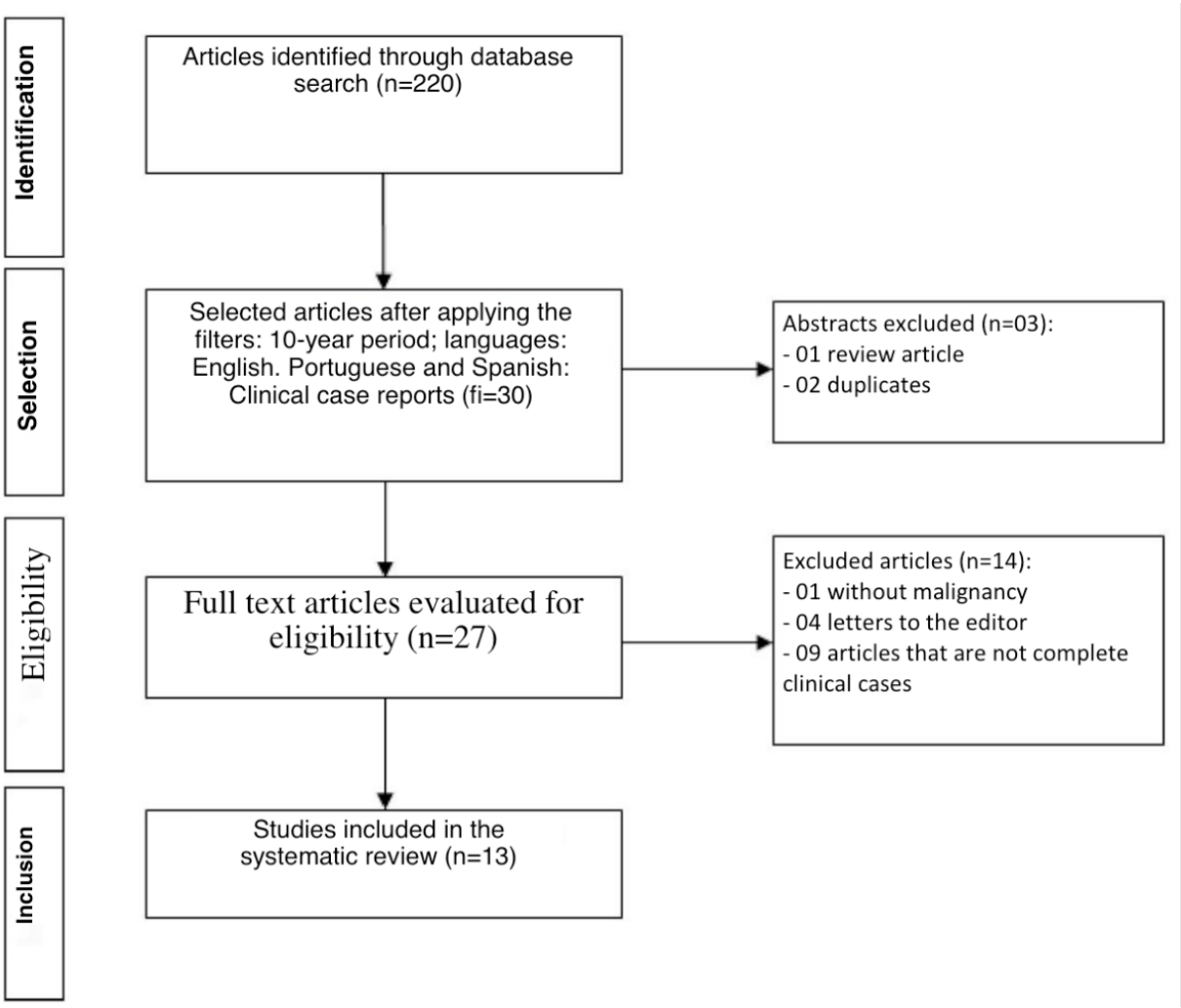

Figura 1-Fluxograma da seleção de artigos da revisão sistemática.

First Author (Year)	Gender and age	Sinai de Leser-Trélat			Malignancy	After CA treatment:	Conclusion
		Place	History	Biopsy			
Fasoldt et al (2012)	M 20	Head, Neck, Back, Arms	Sudden increase	Yes	LLA pre B (recurring)	-	SLT must be considered for investigation of occult malignancy.
Lilly et al (2012)	H 51	Chest, neck, abdomen	Sudden increase	Yes	LMA	-	It suggests the need for further study to understand the etiology of SLT.
Venegas et al (2012)	H 66	Feet	Sudden increase	-	Gastric adenocarcinoma	SLT regresses	It suggests relationship between SLT and underlying malignancy.
Abakka et al (2013)	M 79	Trunk, Face	Sudden increase	-	Leiomyosarcoma	SLT regresses	SLT must be considered for investigation of occult malignancy..
Jepsen et al	H 78	Back, scalp	It appeared in 1 year	Yes	Malignant mesothelioma	-	SLT must be considered for investigation of hidden malignancy
(2014)	M 69	Back, abdomen	It appeared in 4 months	Yes	Pulmonary adenocarcinoma	-	
Onajin et al (2015)	M 4-9	Upper and Lower Extremities	It appeared 1 year	-	Hepatocellular carcinoma	-	It must be considered for investigation of occult malignancy.
Zhang et al (2015)	M 41	Arms, Buttocks	It appeared 6 months ago	Yes	Gastric adenocarcinoma (with multiple metastases)	SLT does not regress	It suggests relationship between SLT and underlying malignancy
Rowe et al (2016)	H 71	Neck, Trunk, Arms, Hands	It appeared in 3 motnhs	-	Mycosis fungoides	-	It suggests relationship between SLT and underlying malignancy.
Narai a et al (2017)	H 84	Chest, Back, Arms	It appeared in 1year	Yes	Cutaneous T lymphoma	SLT regresses	It suggests relationship between SLT and underlying malignancy.
West et al (2018)	M 78	Chest, back, neck	It appeared in 1 month	-	Fallopian tube carcinoma Endometrioid adenocarcinoma.	SLT regresses	It suggests relationship between SLT and underlying malignancy.
Mogollón et al (2018)	F 76	Neck, Thorax, Abdomen, Lower limbs	-	-	Breast cancer	-	SLT must be considered for investigation of occult malignancy..
Nyanti et al (2019)	H 74	Face, Trunk	Undetermined	No	Metastatic renal carcinoma	-	It suggests relationship between SLT and underlying malignancy
Wang et al (2020)	H 68	Face, Arm, Waist	It appeared in 2 months	Yes	Hepatocellular carcinoma	-	Suggests relationship between SLT and underlying malignancy.

Caption: H - Male: M- Female; ALL - Acute Lymphocytic Leukemia; AML - Acute Myeloid Leukemia: TLS - Leser-Trélat Sign: CA- Cancer. Source: Own authorship.

Table 1 - Characterization of selected studies in the systematic review.

First author (Year)	SLT associated to:		First author [Year)	SLT associated to:	
	Itching	Acantose Nigricans		Itching	Acantose Nigricans
Fasoldt et al (2012)	-	**X**	Zhang et al (2015)	**X**	**X**
Lilly et al (2012)	-		Rowe et al (2016)	**X**	-
Venegas et al (2012)	**X**		N arai a et al (2017)	**X**	**X**
Abakka et al (2013)	-		West et al (2018)	-	-
Jepsen et al	-		Mogollon et al (2018)	-	-
(2014)	X		Nyanti et al (2019)	-	-
Onajin et al (2015)	X	X	Wang et al (2020)	-	-

Subtitle: SLT –Signal of Leser-Trélat. **Source:** Own authorship.

Table 2: SLT associated with pruritus and acanthosis nigricans.

DISCUSSION

SLT was first described in 1800[1,4,21] and is a tribute to the German surgeon Edmond Leser and the French Ulysse Trélat[4,5,24]. However, instead of QS, the sign was related to the appearance of multiple eruptive angiomas in cancer patients [2,12,18,25,26]. In 1900, Hollander was the first to describe SQ in association with malignancy, but the names Leser and Trélat remained associated with the disease. [1,2,5,26].

In these cases, the onset of QS lesions, as well as the increase in size and/or quantity, occur suddenly with rapid evolution [1-3]. In general, it is a syndrome more common in the elderly, with a mean age of 61 years and without a predilection for sex. [1,2,15] or breed[1,13,19,23,27]. Therefore, for some authors, SLT is a controversial marker of malignancy. [10,15,22], that is, the controversy stems from the fact that QS are very common as benign findings in the elderly. [13,18,22,23]. Furthermore, there are no clear parameters that define what constitutes rapid QS development [22].

In this review, it was observed that TLS actually affects more elderly people (Table 01), however Fasoldt et al[13] reported the presence of the sign in a 20-year-old male patient, in whom the QS evolved rapidly, associated with acute lymphocytic leukemia (ALL), with the presence of AN in the armpits and groin, thus confirming that the sign despite being more common in the elderly also affects younger people. Reports of TLS in patients in the second decade of life, in association with malignancy, increase the legitimacy of this sign as an accurate predictor of internal malignancy, given the relative rarity of QS in patients of this age [1,27].

Furthermore, the high agreement of TLS resolution with treatment of the underlying malignancy is highly suggestive that it is a true paraneoplastic phenomenon. [28]. Accorgin to Narala et al[5]; Venegas et al[15], West et al[22], after the beginning of cancer treatment, TLS disappeared, without the need for specific treatment for the lesions, supporting the validation of its paraneoplastic behavior. In most cases, with the treatment of the underlying disease, regression of lesions occurs. [1,10,14,15,21,29] which can rarely reappear with cancer recurrence or metastasis. [10,15]. Zhang et al[25] describes the case of a stage IV gastric

adenocarcinoma with metastasis in the right ovary, mediastinal, celiac and retroperitoneal lymph nodes with QS of sudden onset within a period of six months, associated with AN in the axilla, groin spreading through the neck, elbows, umbilicus and anus. Fasoldt et al[13] reports a case of recurrent ALL in which the patient presented SQ in the scalp, face, neck, upper back and upper limbs, of sudden onset, associated with AN in the armpits and groin, making it clear that, although rare, they may have the presence of TLS associated with metastasis or tumor recurrence.

The typical morphology of QS lesions tends to vary widely between patients and may present as macules, plaques [1] and papules [1,26] verrucous-looking [15,26]. They are well-defined lesions and the color varies from skin tone to brown and black [1,15,26] and can cause itching [1,26]. They are usually located on the back and chest and less frequently on the extremities. [1,15,26]. On the back, a symmetrical pattern is often observed, which can resemble a "Christmas tree", "splash" or "raindrop". "[1,12,15].

The exact pathogenesis of the disease is unknown. [12,18,19], but it is believed that there is secretion of tumor products, such as epidermal growth factor (EGFR), which act on epidermal growth receptors, and result in the eruption of multiple lesions [11,15,20,21]. Under normal conditions, EGFR receptors are present in basal keratinocytes and decrease as keratinocytes differentiate in the upper epidermal layers. [13]. However, studies have shown that, in people with TLS, there is an increase in these receptors in both basal and upper keratinocytes, as well as the presence of mutated receptors. [13,18]. Then, these tumor growth factors bind to their skin receptors, stimulate the proliferation of keratinocytes and can lead to the formation of multiple QS[19].

According to this review, 30.7% of cases had AN associated with SLT. Interestingly, many patients who actually exhibit TLS may have, at the same time, another paraneoplastic disease process such asAN[1,19,23,25,26] and itching in the QS region [19]. For some authors, therefore, clues to differentiating early developmental QS from a potential paraneoplastic syndrome include the presence of pruritus and the development of AN[22].

Acanthosis nigricans is characterized by dark patches on the skin, with a thick, velvety texture that usually appear symmetrical in the skin folds, such as the neck, armpits, ankles, knees, between the legs and the palms. It is considered a common dermatosis, usually associated with obesity and insulin resistance. As a paraneoplastic manifestation, it is rare and stands out due to the abrupt onset and rapid spread of hyperpigmented and lichenified skin lesions with a velvety surface. A neoplasm most commonly associated with AN is gastric adenocarcinoma, followed by other tumors in the abdominal cavity and lungs30. Malignant acanthosis nigricans occurs simultaneously in about 20% of cases exhibiting TLS [1,18,20,23,25]. As with TLS, the pathogenesis of malignant acanthosis nigricans is also believed to be related to tumor growth factors secreted by malignancies. However, studies are still limited to a few case reports and further studies are needed to determine the basis of this paraneoplastic dermatosis [22].

The most reported cancers associated with TLS occur in the gastrointestinal tract [2-5,11,12,15-19], such as adenocarcinoma of the stomach, colon and rectum. [7,15,16,23], being more common in the stomach [15,19]. Lymphoproliferative disorders are the second most common type. [2,5,11,15,18,19] and, less frequently, carcinoma of the breast, lung [2,4,7,11,12,19], bladder, kidney [12,18], prostate or nasopharynx [2], gynecological [23], liver or pancreatic [4,12]. In general, the prognosis is not good, as it depends on the type of neoplasm associated, however, most cancers adjacent to the sign behave aggressively. [15,19].

Although these lesions are generally easy to distinguish from other melanocytic neoplasms, histopathological examination may be necessary for differential diagnosis. [1] and it is important to confirm the identity of SQ histologically. [13]. Microscopic findings are well compatible with QS1,31 and may differ a little from case to case, ranging from its typical form to foci of hyperkeratosis with variable degrees of papillomatosis3. However, only 46% of the reports described performing a biopsy for diagnosis. If the patient has symptomatic lesions, they can be removed with cryotherapy, curettage or electrodissection [1,19].

CONCLUSION

Although it is more common in elderly people, TLS can also affect young adults and has a high relationship with gastric adenocarcinoma, hepatocellular and cutaneous T lymphoma. Despite being a rare manifestation and controversial about its relationship with occult malignancies, most studies suggest that this really is a paraneoplastic syndrome, the result of cell proliferation stimulated by tumor cells. Therefore, most of the times, after the diagnosis and treatment of the associated malignancy, the skin lesions regress.

So it is extremely important that clinicians recognize it as an omen for screening for hidden malignancies, especially when associated with more systemic symptoms. It was not possible to verify predilection for sex and race.

AUTHORS' CONTRIBUTION

All authors declare that they contributed equally to the production of this review.

CONFLICTS OF INTEREST

All authors declare that there is no conflict of interest.

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