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REVIEW ARTICLE

Localized Scleroderma: Predisposing and Triggering Factors

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Abstract: The etiology of localized scleroderma remains unclear. The objective of this article is to review different theories of etiology, specifically provocative and predisposing factors for the development of localized scleroderma. The mini-review presents the factors, which may influence the occurrence of localized scleroderma. The genetic predisposition for the development of scleroderma is a relevant characteristic of the disease. Different traumatic factors, viral & bacterial infections, chemical substances, pharmaceutical agents may trigger localized scleroderma. Neoplasia is regarded as a distinct triggering impulse for scleroderma.

Keywords: Chemical agents, Etiology, Genetics, Infections, Localized scleroderma, Malignancy.

INTRODUCTION

Scleroderma is considered a tripartite disease associated with autoimmune, fibroblast and endothelial disorders. The nomenclature of scleroderma has changed dramatically in recent years, with morphoea (localized scleroderma), limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis, and systemic sclerosis sine scleroderma encompassing the currently accepted disease subtypes. Major advances have been made in the molecular studies of localized scleroderma. However, the etiology of the disease remains not yet entirely understood [1]. Many factors are being discussed as provocative for the occurrence of scleroderma: genetic factors, trauma, viral & bacterial infections, toxic substances or pharmaceutical agents [2, 3].

The objective of this article is to summarize different theories of etiology, provocative and predisposing factors for the development of localized scleroderma, using a review of literature.

MATERIALS AND METHODS

The main source of information was Medline Pubmed including original articles, reviews, cases and clinical guidelines. The keywords “localized scleroderma” and ”etiology” were used. 360 publications from 2010 to September 2016 were analyzed. We selected 95 publications that presented the provocative & predisposing factors for localized scleroderma development.

INCLUSION AND EXCLUSION CRITERIA

The review articles, retrospective cohort studies, case series and case reports were included. The articles published before 2010 were excluded.

RESULTS

The results are summarized in Table **1**.

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The Genetic Predisposition

On the one hand, the genetic predisposition to localized scleroderma is examined. Family cases of localized scleroderma are known. For example, a case of localized scleroderma affecting both a father and a son was presented by Pham CM & Browning JC, (2010) [4].

In the genesis of scleroderma on the other hand, X chromosome monosomy is considered important by Karaca NE & colleagues, (2011) [5]. A case of female monozygotic twins who presented co-existence of localized scleroderma and lichen sclerosis was described. Co-existence of these diseases in monozygotic twins indicated the possible genetic contribution to the genesis of localized scleroderma and lichen sclerosis [6]. The influence of HLA haplotypes is crucial for various molecular mechanisms, leading to fibrosis in both the skin and the underlying connective tissue [7]. The specific HLA class I and class II alleles are associated with localized scleroderma and are also likely to be associated with generalized and linear subtypes of localized scleroderma. Jacobe H & colleagues, (2014) found the strongest associations with DRB1*04:04 and HLA-B*37 among the class 1 alleles [8].

Table 1. Localized scleroderma: predisposing & triggering factors.

Triggers	Factors	Authors
genetic predisposition:	family cases	Pham CM, Browning JC.(2010) [4],Lis- Święty A, Mierzwińska K, Wodok- Wieczorek K, Widuchowska M, Brzezińska- Wcisło L.(2014) [6]
	X-chromosome monosomy	Karaca NE, Aksu G, Karaca E, Tuzun F, Gunes AT, Ozkinay F, Kutukculer N.(2011) [5]
	the influence of HLA haplotypes	Canady J., Karrer S., Fleck M., Bosserhoff A.K.(2013) [7], Jacobe H, Ahn C, Arnett FC, Reveille JD. (2014) [8]
endocrine changes:	pregnancy	Noda S, Asano Y, Ashida R, Tomita M, Kawashima T, Sato S.(2011) [9], Benchat L, Mernissi F.Z.(2013) [10],Wong B, Pilouras P, Mortimore R, Zonta M., Tucker S.(2015) [11]
	thyroid dysfunctions	Bonilla- Abadia F., Muñoz- Buitron E, Ochoa CD, Carrascal E., Cañas CA (2012) [13],Hassan I., Arif T, Anwar P.(2014) [12]
	diabetes mellitus	Firoz EF, Kamino H, Lehman TJ, Orlow SJ(2010) [22]
trauma:	physical injuries	Fett N, Werth VP. (2011) [1], Browning JC. (2013) [29], Arif T.*et al.*(2015) [23], Arif T., Majid I.(2015) [24],, Careta MF, Romiti R(2015) [28],Touloei K, Wiener A, Glick BP. (2015) [31],Wolf R, Wolf D, Ruocco V, Ruocco E. (2015) [26]
	mechanical compression by clothes	Grabell D, Hsieh C, Andrew R, Martires K, Kim A, Vasquez R, Jacobe H. (2014) [25]
	wearing slimbelt	Arif T.*et al.*(2015) [27]
	injection	Ueda T, Niiyama S, Amoh Y, Katsuoka K. (2010) [33]
infections:	cytomegalovirus	Goulabchand R, Khellaf L, Forestier A, Costes V, Foulongne V, le Quellec A, Guilpain P [34].
	varicella	Patel H, Thakkar C, Patel K.(2010) [35], Qu T, Fang K. (2014) [36]
	HIV	Mosquera JA, Ojea R, Navarro C. (2010) [37]
	borrelia infection	Espinoza-León F, Arocha F, Hassanhi M, Arévalo J.(2010) [38], Zollinger T, Mertz KD, Schmid M, Schmitt A, Pfaltz M, Kempf W. (2010) [47], Santos M, Ribeiro- Rodrigues R, Talhari C, Ferreira LC, Zelger B, Talhari S. (2011) [39],Moniuszko A, Gińdzieńska-Sieśkiewicz E, Pancewicz SA, Czupryna P, Zajkowska J, Sierakowski S. (2012) [40],Miglino B, Viana M, Zavattaro E, Bonin S, Valente G, Colombo E. (2012) [41],Miller K, Lehrhoff S, Fischer M, Meehan S, Latkowski JA(2012) [42], Inci R, Inci MF, Ozkan F, Oztürk P. (2012) [43], di Meo N, Stinco G, Nan K, Pinzani C, Trevisan G. (2015) [44],Aberer E, Wutte N,(2016) [45],Trevisan G., Trevisini S., di Meo N., (2016) [46], Gutiérrez- Gómez C, Godínez- Hana AL, García- Hernández M, Suárez-Roa M deL, Toussaint-Caire S, Vega- Memije E, Gutiérrez- Mendoza D, Pérez-Dosal M, Medina-Dela Garza CE(2014) [48],Verberkt RM, Janssen M, Wesseling J. (2014) [49]
vaccinations:	hepatitis B	Benmously Mlika R, Kenani N, Badri T, Hammami H, Hichri J, Haouet S, Mokhtar I, Fenniche S. (2010) [50]
	diphtheria/tetanus/pertussis	Khaled A, Kharfi M, Zaouek A, Rameh S, Zermani R, Fazaa B, Kamoun MR. (2012) [51]
	measles/mumps/rubella	Weibel L. (2012) [52]
	pneumococcal vaccination	Viladomiu Edel A, Valls AT, Zabaleta BA, Moreno AJ, Pérez NO(2014) [53]
chemical agents	pesticides	Sozeri B, Gulez N, Aksu G, Kutukculer N, Akalın T, Kandiloglu G. (2012) [54]
	silicone	Kivity S, Katz M, Langevitz P, Eshed I, Olchovski D, Barzilai A. (2012) [55]
	adjuvants	Frances L, Leiva- Salinas M, Angelica MB, Marin I, Silvestre JF. (2014) [56]

(Table 1) contd.....

Triggers	Factors	Authors
pharmaceutical agents	valproate	Aslan A.,Kotoroglu G.,Sözeri B.,Kurugöl Z. (2014) [59]
	TNF-alpha inhibitors	Mattozzi C, Richetta AG, Cantisani C, Giancristoforo S, D'Epiro S, Gonzalez Serva A, Viola F, Cucchiara S, Calvieri S. (2010) [61]
		Ramírez J, Hernández MV, Galve J, Cañete JD, Sanmartí R(2012) [62],Stewart FA, Gavino AC, Elewski BE. (2013) [63]
	vitamin B_{12}	Verdelli A, Antiga E, Bonciolini V, Bonciani D, Volpi W, Caproni M. (2014) [60]
	vitamin K	Lembo S, Megna M, Balato A, Balato N. (2012) [64]
	hydroxyurea	García- Martínez FJ, García- Gavín J, Alvarez-Pérez A, Alonso-González J, Ginarte M, Toribio J. (2012) [65]
	antifolates	Corbaux C, Marie J, Meraud JP, Lacroix S, Delhoume JY, Jouary T, Madoui S. (2015) [66]
	taxanes	Pedersen JV, Jensen S, Krarup-Hansen A, Riis L. (2010) [71], Konishi Y, Sato H, Sato N, Fujimoto T, Fukuda J, Tanaka T. (2010) [72], Torregrosa JL, Fernández M, Garcías J, Pérez A. (2014) [73]
	balicatib	Rünger TM, Adami S, Benhamou CL, Czerwiński E, Farrerons J, Kendler DL, Mindeholm L, Realdi G, Roux C, Smith V. (2012) [74]
Coexistence of scleroderma with oncologic diseases:	multiple myeloma	Gajendra S., Gupta R, Gupta R, Kumar L. (2013) [79]
	malignant carcinoid syndrome	Becher G, Leman J. (2013) [79]
	odontogenic carcinoma	McNamara PH, Toner M, Kearns G, Keohane C, Daly P, Doherty CP. (2013) [78]
	squamous cell carcinoma	Saleh DB, Williams AM, Smith IM.(2011) [80], Durčanská V, Jedličková H, Sláma O, Velecký L, Březinová E, Vašků V. (2014) [81], Grewal I, Khan O, Davis W. (2014) [82]
	localized scleroderma induced by radiotherapy prescribed for breast cancer	Akay BN, Sanli H, Heper AO. (2010) [94], de Giorgi V, Santi R, Grazzini M, Papi F, Gori A, Rossari S, Massi D, Lotti T.(2010) [91], Laetsch B, Hofer T, Lombriser N, Lautenschlager S. (2011) [85], Wernicke AG, Goltser Y, Trichter S, Sabbas A, Gaan J, Swistel AJ, Magro CM. (2011) [86], Llenas J, Bringas A, Nocito J, Gómez Zanni S, Campana R, Papa M. (2012) [87], Newland K, Marshman G. (2012) [88], Lim D, Johnston S, Novakovic L, Fearfield L. (2014) [89], Reynolds TD, Knights SE. (2014) [84], Vigneron C, Bauer N, Waisse W, Keller A, Pop M, Clavier JB, Salze P, Noël G. (2014) [93], Spalek M, Jonska- Gmyrek J, Gałecki J. (2015) [92], Yanaba K, Umezawa Y, Nakagawa H. . (2015) [90]

The Endocrine Changes

The endocrine changes are considered contributing to the development of autoimmune disease. It is well known that different types of scleroderma can follow pregnancy [9 - 11]. L. Benchat & F.Z. Mernissi, (2013) suppose that pregnancy can be a predisposing factor of localized scleroderma because of microchimerism. According to the opinion of L. Benchat & F.Z. Mernissi, (2013), chimeric cells are non-self cells transferred from fetus to mother during pregnancy [10].

Wong B & colleagues, (2015) reported a case of linear localized scleroderma in a 21- year old woman in her early first trimester of pregnancy. The patient suffered from Graves' disease and was also cytomegalovirus positive. The case highlighted the combination of risk factors [11].

Hassan I & colleagues, (2014) examined thyroid dysfunctions in morphoea. The levels of thyroid stimulating hormone were elevated with 41.2% patients [12].

Bonilla-Abadia F.& colleagues,(2012) reported a case presenting an association of localized scleroderma, vitiligo, autoimmune thyroidism, pneumonitis, autoimmune thrombocytopenic purpura and central nervous system vasculitis. Localized scleroderma seemed to be a part of multiple autoimmune syndrome [13]. There are many reports of localized scleroderma associated with vitiligo in patients with thyroid disfunction [14 - 16]. Association of localized scleroderma with other autoimmune diseases emphasizes autoimmune etiology of localized scleroderma.

The typical association with other autoimmune diseases, as seen in generalized vitiligo, seems to be significantly less in segmental vitiligo [17].

However, there are some reports of localized scleroderma associated with vitiligo in patients without thyroid disfunction [18 - 20]. Apart from these surveys, a case of segmental vitiligo involving the left side of the trunk and left upper limb with segmental morphea involving the right side of trunk and right upper limb was present in an 18-year old

girl. A history of type II diabetes mellitus in the father was elicited [21].

Localized scleroderma was diagnosed in diabetes mellitus patients, as well [22].

Trauma

Different physical injuries are known to be a triggering factor for scleroderma development. Arif T. & colleagues, (2015) reported a case of linear localized scleroderma in a 26-year old woman with a lesion on the frontal and forehead regions. The patient mentioned that she had had a trauma at the same site six years back [23]. Trauma was the triggering factor as well in the development of linear scleroderma in a 32-year old woman. The skin lesion remained localized to the forehead during the subsequent 12 years and then the new lesions progressed down. The question of the possibility of quiescent period in the development of scleroderma was discussed [24]. The cross-sectional analysis of the localized scleroderma in adults and children cohort (MAC) was performed by Grabell D & colleagues, (2014) [25]. 52 (16%) among 329 patients in the MAC cohort had trauma-associated lesions at the onset of disease. Patients with lesions in an isotopic distribution had greater clinical severity as measured by a clinical outcome measure [25]. Another cross-sectional survey of the MAC cohort emphasized the role of skin trauma [26]. The mechanical compression from clothes [27], particularly slim belt, is discussed [27]. The appearance of localized scleroderma lesions after fluoroscopy, laparotomy and rhinoplasty was outlined [28 - 30].

A case of a morphea profunda in a 50-year-old woman with a history of trauma sustained in an automobile accident was reported [31]. Vibration can influence the appearance of scleroderma, as well [32]. Ueda T & colleagues, (2010) presented a case of linear scleroderma developed approximately 3 months after contusion and treatment by local injection of mepivacaine hydrochloride [33].

Viral and Bacterial Infections

A potential triggering role of CMV primary infection in the development of scleroderma is discussed [34]. Parry-Romberg syndrome, frequently associated with localized scleroderma, is known to be provoked by viral infections [35]. Some cases of localized scleroderma following varicella were described earlier. Qu T & Fang K., (2014) presented another possible connection of localized scleroderma with Varicella Zoster. A case of bullous morphea arising at the site of a healed herpes zoster was described [36]. HIV infection associated with scleroderma is also known, and the immunodeficient status may be predisposing for localized scleroderma development in these cases [37].

The question of the role of Borrelia infection still remains controversial [38 - 49]. Different diagnostic methods may be crucial for the estimation of the Borrelia significance. For example, the investigation performed in Mexico showed a lack of IgG antibody seropositivity to Borrelia burgdorferi in patients with Parry-Romberg syndrome and linear morphea en coup de sabre [48]. The results of PCR-based studies do not argue for a significant association of B. burgdorferi sensu lato with localized scleroderma [39]. On the other hand, Verberkt RM and colleagues, (2014) emphasized that focus floating microscopy proved to be more sensitive than polymerase chain reaction and observed to be nearly equally specific [49].

Not only infections, but also vaccination can induce scleroderma [50 - 53]. Morphoea profunda after hepatitis B vaccination was described [50]. In another case, morphoea profunda appeared 3 months after a third dose of diphtheria-tetanus-pertussis vaccine [51]. Measles/mumps/rubella vaccine is also known as a factor, which may be provocative for the development of localized scleroderma [52]. Morphoea profunda after pneumococcal vaccination was also described [53].

Chemical and Pharmaceutical Agents

The incidences of localized scleroderma and systemic sclerosis have increased in patients with preceding exposure to particular substances. Scleroderma can be induced by some chemical agents, for example pesticides containing malathion and diniconazole [54]. Localized scleroderma is occasionally linked with exposure to chemical compounds such as silicone [55]. The disease was described as a sign of autoimmune syndrome induced by adjuvants [56].

Valproate is known to provoke the development of autoimmune diseases [57, 58]. The exposure to valproate can cause sclerodermal skin changes [59].

Several classes of drugs seem to be capable of inducing or exacerbating localized scleroderma [60]. The treatment with TNF-alpha inhibitors can induce localized scleroderma development [61 - 63]. Scleroderma-like cutaneous changes may be caused by vitamin B_{12} [60], vitamin K [64] and hydroxyurea [65]. On the other hand, patients with

autoimmune diseases are diagnosed with increased frequencies of some cancers, which may depend on treatment.

Moreover the treatment of oncologic diseases can also provoke the development of localized scleroderma. The antifolates may cause scleroderma-like induration of the skin [66]. Bleomycin can also cause scleroderma-like changes and nowadays is used for mouse model of scleroderma [67 - 70]. The taxanes can also cause scleroderma-like lesions [71 - 73]. The usage of cathepsin K inhibitor balicatib has an adverse effect of skin hardening and morphoea-like changes, as well [74].

Scleroderma and Oncologic Diseases

The autoimmune diseases are associated with an increased risk of malignancy [75]. Dysregulation of the immune system underlies systemic sclerosis [76]. In localized scleroderma [77, 78] indicated to possible association with oncologic diseases.

Co-existence of scleroderma and multiple myeloma was described by Gajendra S. & colleagues, (2013) [79]. Squamous cell carcinoma is known to develop in localized scleroderma patients [80 - 82]. Paraneoplastic scleroderma is described, as well [83, 84]. Jedlickova H & colleagues, (2016) regard neoplasia as a distinct triggering impulse for scleroderma. The patients with paraneoplastic scleroderma were characterized by older age, sudden onset, diffuse thickening of the skin, and/or generalized morphea with a concurrent neoplastic disease. When the tumor treatment was successful, skin changes regressed. Further studies may confirm the true link between scleroderma and malignancy [83].

Several cases describe the development of localized scleroderma induced by radiotherapy prescribed for breast cancer [84 - 94]. De Giorgi V & colleagues, (2010) described synchronous cutaneous angiosarcoma, melanoma and localized scleroderma, which developed within 14 years after radiotherapy of breast carcinoma [91]. Spalek M & colleagues, (2015) presented the literature review that analyzed 66 cases reported in the literature since 1989. The clinical appearance often includes pain and disfiguration of affected area, which may influence the patient's quality of life. There is no clear connection between the radiotherapy dose, the fractionation scheme, the use of a boost, age, the presence of other dermatological conditions or other connective tissue diseases and the occurrence of radiation-induced localized scleroderma [92]. Vigneron C and colleagues, (2014) believes that radiation-induced localized scleroderma is unrecognized and under-diagnosed [93]. The postirradiation linear morphea was described in a 74-year-old woman who was treated with radiotherapy for endometrial carcinoma. About 3,5 years after the first dose of radiotherapy, the patient developed linear localized sclerodermastarting from the radiation port and affecting distant, nonirradiated skin [94].

DISCUSSION

The genetic predisposition to localized scleroderma has been investigated in the recent years [4 - 8]. The triggering factors in genetically predisposed individuals might initially lead to an immunologically triggered release of pro-inflammatory cytokines, resulting in a profound dysregulation of the connective tissue metabolism and ultimately to induction of fibrosis [95]. Actually, there are no obligatory triggering factors, but each group of them can be crucial for a certain group of patients.

The physiological and pathological endocrine changes can precede the appearance of localized scleroderma [9 - 14]. The role of hormonal upregulation is being discussed as a possible trigger of autoimmunity [12 - 14]. As for pregnancy, it can be a predisposing factor of localized scleroderma because of microchimerism. The chimeric cells are non-self cells transferred from fetus to mother during pregnancy [10].

The trauma-associated lesions at the onset of disease were often mentioned [25 - 33]. The post-traumatic neurovascular changes are possible predisposing factors for the development of localized scleroderma.

The viral and bacterial infections are often discussed as provocative for the onset of autoimmune diseases. The role of Borrelia infection still remains unclear. The controversial opinions are presented in [38 - 49]. The different viral infections are also known to precede the appearance of localized scleroderma [34 - 37]. Anyhow, the viral and bacterial infections are not obligatory for the development of localized scleroderma, but seem to be the triggering factors. The different vaccinations are likely to be triggers, as well [50 - 53].

The localized scleroderma can be induced by some chemical agents (pesticides containing malathion and diniconazole, silicone, *etc.*) [54 - 56]. Different groups of pharmaceutical agents (valproate, TNF-alpha inhibitors, vitamin B_{12}, vitamin K, hydroxyurea, antifolates, taxanes *etc.*) can also provoke the onset of localized scleroderma

[57 - 74]. We can suppose that the administration of these drugs might initially lead to an immunologically triggered release of pro-inflammatory cytokines and further development of localized scleroderma.

The patients with localized scleroderma are predisposed to oncologic diseases [77, 78], and vice versa, the development of localized scleroderma can be induced by radiotherapy prescribed for breast cancer [84 - 94]. Some cases of co-existence of localized scleroderma and other malignancies were also described [75 - 82]. The link between fibrosis, tumor progression, and cancer metastasis is being investigated. The impact of immune changes cannot be denied, either.

CONCLUSION

Analysing the publications on localized scleroderma, we can see the following predisposing and trigger factors:

- the genetic predisposition
- trauma
- some chemical substances (marathon, diniconazole, silicone)
- the pharmaceutical agents (valproate, TNF-alpha inhibitors, vitamin B_{12}, vitamin K, hydroxyurea, antifolates, taxanes)
- Borrelia burgdorferi and viral infections
- vaccinations
- radiotherapy for breast cancer
- the possibility of the development of paraneoplastic scleroderma

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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