Section A-Research paper

A Brief Insight about Syringoma Variants and its Differential Diagnosis

Mohamed Metwalli Abdel Naby[1], Kamal Ahmed El Kashishy[2], Mohamed Mahmoud Nasr[1], Nehal Anwar Ezzat[1]

1 Dermatology, Venereology and Andrology Department, Faculty of Medicine - Zagazig University, Egypt

2 Pathology Department, Faculty of Medicine - Zagazig University, Egypt

Email: nehalanwar50@gmail.com, n.ismael22@medicine.zu.edu.eg

Article History: Received 10th June, Accepted 5th July, published online 10th July 2023

Abstract

Background: Syringomas are benign adnexal tumors of eccrine origin, with four principal clinical variants. In eruptive syringoma, a rare variant first described by Jacquet and Darier in 1987, the lesions occur in large numbers and in successive crops on the anterior chest, neck, upper abdomen, axillae, and the periumbilical region at puberty or during childhood. More rarely, cases with wider involvement of the body have also been reported. It occurs more frequently among women. The lesions consist of asymptomatic multiple small firm yellow-brown-colored papules, that typically present in a bilateral, symmetrical distribution, but there have been reports of unilateral, unilateral nevoid, bathing trunk and generalized distributions. Clinically, it may be mistaken for acne vulgaris, sebaceous hyperplasia, milia, lichen planus, eruptive xanthoma, urticaria pigmentosa, hidrocystoma, trichoepithelioma and xanthelasma on the face and granuloma annular on the trunk. Definitive diagnosis can be made on histological examination, because syringomas demonstrate distinctive histopathological features. Syringomas on the face clinically mimic trichoepitheliomas and BCC, whereas eyelid lesions can be mistaken for xanthelasma. Eruptive syringomas may resemble disseminated granuloma annulare, especially on the trunk.

Keywords: Syringoma, Differential Diagnosis

DOI: 10.53555/ecb/2023.12.Si12.236

Introduction

Syingoma is a benign adnexal tumor that is derived from intra epidermal eccrine duct. It is commonly seen in periorbital area as multiple, small, soft or firm papules from 1 to 3 mm in diameter. It can also develop on the scalp, neck, anterior chest. axilla, upper abdomen, extremities, buttock and genetalia **(1)**.

Development of syringomas occurs when sweat duct cells in the outermost layer of the skin overgrow or sweat glands overact forming tumors or abnormal tissue growths **(2)**

Syringoma was described for the first time by **Kaposi (3)** as lymphangioma tuberosum multiplex**.**

The intraepidermal eccrine sweat gland nature of syringoma was confirmed by electron microscopy and histochemistry **(4)**.

Epidemiology of syringoma:

Syringoma is more common in females than males with a ratio of 2:1. It occurs usually around puberty or the third and fourth decades of life, Prepubertal eruptions tend to occur mainly in the apocrine sites such as axilla that are rarely affected in post pubertal subjects **(5)**.

Syringoma occurs mainly in white individuals but also was found in black females. It is more common in Asians than other races. The incidence of syringoma is common in Down syndrome occurring mainly in the eyelid **(6)**.

Etiology and pathogenesis of syringoma:

The etiology of most cases of syringoma is unknown and the pathogenesis and the cause of inflammation that occurs around proliferated eccrine glands in cases of syringoma are also unknown. So there are many theories about the etiopathogenesis of syringoma **(7)**.

1- Neoplastic factor:

Eruptive syringoma represents a hyperplastic response of the eccrine duct to an inflammatory reaction **(7)**.

2- Non-neoplastic factor:

Eruptive syringoma is not true neoplasm, but rather a hyperplastic reaction of the eccrine ducts that results in proliferative changes after an inflammatory process of the upper portion of the eccrine duct. **(7)**.

3- Environmental factor:

There are effects of high altitude on the sweat apparatus and a mast cell-mediated pathogenetic mechanism **(8)**.

4- Familial factor

The familial occurrence of syringoma is well documented in many families of diverse ethnic origin. In all cases the mode of inheritance is autosomal dominant **(1)**.

5- Hormonal factor:

Syringoma is under estrogen or progesterone as it is more common in women and worsened during pregnancy and menstruation. Some cases have been reported, particularly in the vulvar region, recurrently arising in young women alter puberty with pruritus and exacerbating during menstruation **(9)**

Timpanidis et al. (10) proposed that the demonstration of progesterone-positive receptor, supported the theory that hormonal control might be important in the pathogenesis of eruptive syringoma.

On the contrary, it was mentioned by **Lee et al. (1)** that syringoma is not under the effect of estrogen and progesterone, and if syringoma is influenced by estrogen and progesterone, the hormonal control is not through the high levels of hormonal receptors.

6- Iatrogenic factor:

It was reported that a case of post pubertal eruptive syringoma elicited with antiepileptic drugs. It is well known that antiepileptic drugs induce hepatic microsomal enzymes and interact with hormonal contraceptive by increasing estrogen's metabolism and protein binding of progesterone results with the decrease of the concentration of both hormones. **(9)**

Clinical variants of syringoma:

There are four types of syringomas: local type, eruptive type, Down syndrome associated type, and familial type. Among them, the local type is the most common, which is identified by symmetrical papules around the eyes. However, it's often ignored by patients due to the small scope of influence, inconspicuous skin lesions, and no symptoms **(11)**.

Other variants have been reported such as linear, vulvar, penile, scalp, acral, milia-like, clear cell and plaque type syringoma **(11)**.

Syringoma rarely shows the unilateral or linear distribution. There have been only 4 reports of unilateral linear syringoma, all involving the upper trunk and limb. linear syringoma usually presents clinically quite similar to ordinary syringoma **(9)**

1.Eruptive syringoma:

Eruptive syringomas is a rare variant compared with the other types, but it brings great stress to patients due to obvious skin lesions, large scope of influence, and high misdiagnosis rate. Eruptive syringmas generally occurs in adolescence or early adulthood and has also been reported in children and the elderly. It manifests as a sudden, massive appearance that affects two or more anatomical parts of the body, such as the anterior chest and abdomen **(11).**

More seldom cases with broader involvement of the body have been reported. It happens more often among women. The lesions consist of asymptomatic multiple small firm yellow-brown colored papules that characteristically present in a lateral, symmetrical distribution but there have been reports of unilateral, unilateral nevoid, bathing trunk and generalized distributions **(5)**.

It may be mistaken clinically for acne vulgaris, sebaceous hyperplasia, milia, lichen planus, eruptive xanthoma, urticaria pigmentosa, or hidrocystoma **(12)**.

2.Familial syringoma:

The familial incidence of disseminated syringoma inherited as an autosomal dominant trait was described under the term asymptomatic eruptive hidradenoma. Since then autosomal dominantly inherited familial syringoma has been frequently described, signifying that this disorder most probably represents a monogenetic entity **(13).**

3.Syringoma and Down syndrome:

The occurrence of syringoma in Down syndrome has been reported to be nearly 30 times greater than in the general population. Syringoma of the eye lids are nearly exclusive to Down syndrome patients **(14)**.

4.Clear cell syringoma:

Clear cell syringoma was first described by **Headington et al. in (15)** it has been known to be one of the dermatological diseases accompanying diabetes mellitus. In most cases, numerous miliary-sized papules are seen on both eyelids. However, in some cases the papules become large than ordinary syringoma.

Though clear cells are occasionally noted in ordinary syringoma, the cells in clear cell syringoma are inclined to proliferate and have a smaller nucleus and dense chromatin **(16)**.

The pathogenesis of clear cell syringoma is unknown. The PAS-positive substance in the clear cell is considered to be glycogen. In some cases, Phosphorylase activity in clear cell syringoma was reported to be suppressed **(17)**.

Headington et al. (15) mentioned that the clear cells undergo glycogenesis because of a relative deficiency in phosphorylase.

On the contrary, **Saitoh et al. (16)** claimed that phosphorylase activity in syringoma may be normal, but elevated glucose levels in diabetics may suppress the activity of phosphorylase**.**

Ohnishi et al. (18) established that clear cell syringoma displaced differentiation into the transitional portion between the acrosyringium and the dermal duct, as in conventional syringoma. They concluded that clear cell syringoma is a metabolic variant of ordinary syringoma.

5.Vulvular syringoma:

The vulvar syringoma was first reported by **Carneiro et al. (19).** It may be localized or associated with extra-genital lesions. The existence of similar lesions in other parts of the body may help diagnosis. **Choi et al., (20)** reported that though syringoma is asymptomatic in most cases, some patients may suffer from itching and pruritis in both genital and extra-genital syringoma

Actually, most of the reported cases of vulvular syringoma were known because of the pruritus. True incidence of symptomatic vulvular syringoma may be underrated because asymptomatic lesions are missed by physicians. The main presentation of vulvular syringoma is the presence of symmetrically distributed multiple skin-coloured papules on the labia majora of the vulva, its polypoid presentation is very rare **(9)**

Syringoma is mainly asymptomatic and permanent, but it may have cyclic changes in its size and symptoms during the premenstrual period, pregnancy and with the usage of oral contraceptives **(20)**.

6.Milium-like syringoma:

It is an uncommon variant of syringoma. The cases that have been reported until now are very few. It can be deceptive to dermatologists or even unnoticed by pathologists. It is possible that the superficially situated ductal lumina in syringoma undergo dilatation due to occlusion of the ducts, resulting in keratin accumulation, to a degree that look like milia clinically **(21).**

According to this, we have no differentiation between milia and syringoma. Syringoma was considered a tumor derived from acrosyringeal eccrine ducts. Some authors further propose that it might be a differentiation of lower acrosyringium or transitional portion between acrosyringium and dermal duct **(4)**.

Milia are classified as primary or secondary. It occurs on the face in susceptible individuals, primary milia are derived from the lowermost portion of the infundibulum of vellus hairs at the level of sebaceous duct. Secondary milia, occurs after bulous diseases, trauma or dermabrasion and have the same histologic appearance. They may develop from a hair follicle, sebaceous duct, sweat duct or epidermis **(21).**

7.Acral syringoma:

Acral syringoma appeared as symmetrical, gathered, faintly pigmented, papules limited to the dorsum of both bands. This clinical presentation should be encompassed in the differential diagnosis of papular lesions on the bands including lichen planus, verruca plana, lichenoid contract dermatitis, Acrokeratosis verruciformis, molluscum contagiosum. Acral position is very rare according to cases reported in the dermatological literature which were only five cases **(22)**.

Dermoscopy of syringoma:

Dermoscopic features of syringoma are a delicate and very faint brown pigment network and multifocal hypopigmented areas. also it may appear as incomplete pigment network with faint erythema**.** Other dermoscopic features are tiny whitish dots coexisting with fine reticular brown lines on the background superimposed by demarcated reticular vascular network **(23).**

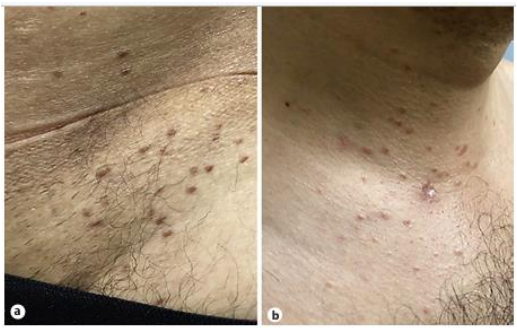

Fig. 1. Eruptive syringoma. Clinical images. **a** Brownish papular lesions located on the inguinal region. **b** Erythematous papules on the neck **(24).**

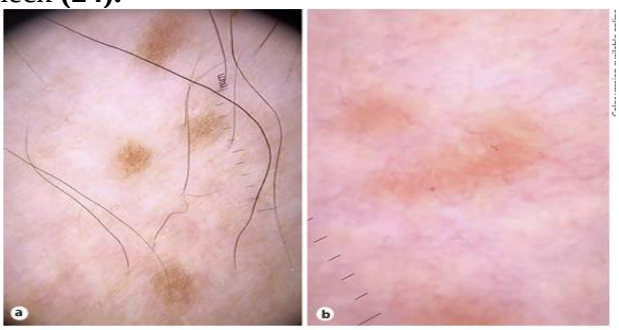

Fig.2 Dermoscopy of eruptive syringoma. **a** Thin reticular network. **b** A reticular vascular network on a faint background. with multifocal hypopigmented areas **(24).**

Histopathology and immunohistochemistry:

Final diagnosis of syringoma can be made on histopathological examination. Haematoxylin-eosin stain (H and E) shows multiple small ducts within the dermis. The ducts are lined by two rows of epithelial cells with comma-like tail or tadpole appearance. Ductal lumina are filled with an amorphous, Periodic-Acid-Schiff (PAS) positive material. Histochemical and electron microscopic findings have confirmed that syringoma represent adenoma of eccrine ducts. Some additional findings, acanthosis, hyperpigmentation of basal keratinocytes, keratin cyst/milia-like structures and telangectasia of superficial vessels **(25).**

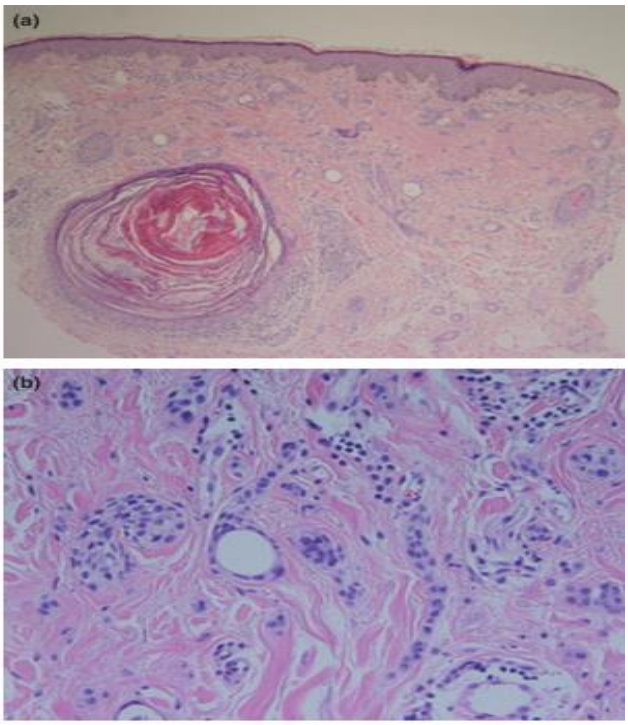

Figure 3 Light microscopic features of syringoma. **(a)**Multiple cystic structures, ducts, and epithelial strands embedded in the fibrous stroma. Also basal hyperpigmentation and a keratin-filled cyst (hematoxylin and eosin, x40). **(b)** The ducts are lined by two rows of epithelial cells. With small comma-like configurations giving a tadpole appearance (hematoxylin and eosin,x200) **(26).**

Immunohistological investigations suggest an eccrine duct origin **(27)**. There is a dispute over the eccrine origin of syringoma because most are situated in apocrine rich areas such as the lower eyelid, axillae and abdomen and scarcely happening in only eccrine areas like the palms and soles **(27)**. However, it has been shown by immunohistochemical studies the existence of several enzymes comprising aminophosphorylase, succinic dehydrogenease, leucine aminopeptidase and PAS-positive material all of which are more greatly concentrated inside the eccrine ducts as compared to apocrine **(4)**.

Moreover, solid strands observed in syringomas originate from the outer cells of the two layers of cells that compose the lower epidermal duct or the transitional portion between the intraepidermal duct and dermal duct in the normal eccrine structure so the solid strands stain for epithelial membrane antigen (EMA) and cytokeratin 5 (CK5), as did the outer cells of the ductal structure. However, the solid strands do not stain with carcino embryonic antigen (CEA) **(26).**

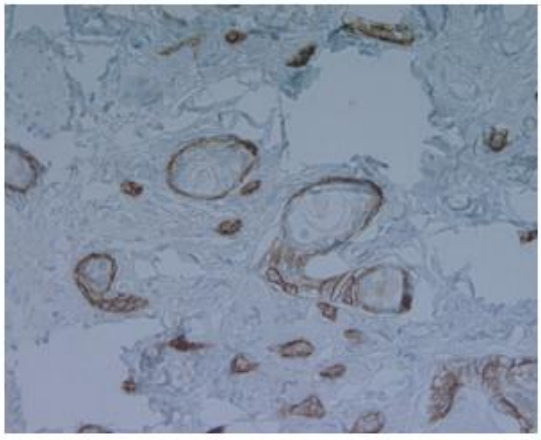

Figure 4 Positive staining for EMA is visible in peripheral cells and epithelial strands. The luminal cells of the duct did not stain positive for EMA (x400) **(26).**

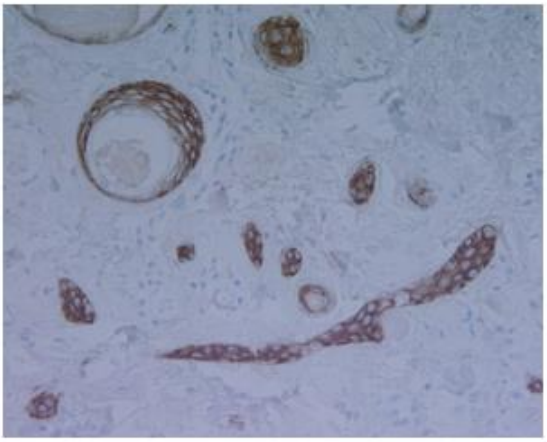

Figure 5 Distribution of cytokeratin (CK5) in syringomas. Antibody against CK5: the outer cells and epithelial strands are all strong positive. The luminal cells of the duct did not stain positive for CK5 (x400)

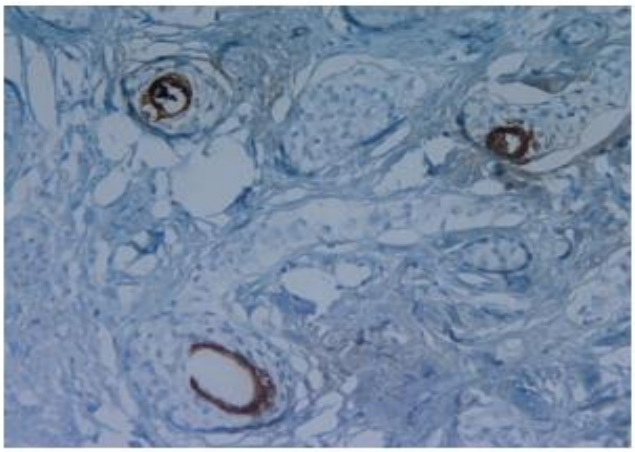

Figure 6 Distribution of carcinoembryonic antigen (CEA) in syringomas. Strong positive staining for CEA is visible in the inner cells as well as in secretions within the lumina. The outer cells of the ducts and epithelial strands did not stain positive for CEA (x400) **(26).**

Carcinoembryonic antigen

Carcinoembryonic antigen and a number of glycoproteins related to CEA have been demonstrated in normal or neoplastic epithelia of the gut, liver, lung, breast, and other tissues. These glycoproteins were identified as products of a complex gene family that encodes the classical 180-kDa CEA, the 160 kDa biliary glycoprotcin (BGP), and the non specific cross-reacting antigens (NCA) of 95 KDa (NCA-95) and 90 kDa (NCA-90). The CEA glycoproteins and their splice variants differ in size, number of immunoglobulin domains, posttranslational modification, membrane anchorage, and glycosylation **(13).**

Cytokeratins

In human epithelia, 19 different cytokeratin polypeptides have so far been described. Different sets of polypeptides of this protein family are expressed in different types of epithelial cells, and three main categories of cytokeratin patterns can be distinguished: (1) patterns of many stratified squamous epithelia are characterized by the presence of basic cytokeratins (numbers: 1-6) and the acidic components(numbers: 9&17) (2) one-layered (simple) epithelia contain two to four members of polypeptide group (numbers: 7, 8, 18&19) and lack basic components; (3) certain epithelia such as respiratory or several glandular epithelia reveal complex patterns containing components of both the first and the second category **(28).**

Epithelial membrane antigen

The epithelial membrane antigen has been described in immunological terms and has been shown immunohistochemically to be present on a variety of human non-squamous epithelial surfaces. It is a valuable

marker in diagnostic tumour pathology and enables the detection of small deposits of malignant cells in organs such as liver and bone marrow. Its discovery in soluble form in human milk has enabled a purification of the antigen from this source. Although purification causes a general reduction in size, the antigen remains heterogeneous **(29).**

Carbohydrate forms the major component of the antigen with galactose and N-acetylglucosamine as the two major sugars. The protein content of EMA is low and shows considerable variation in amino acid composition from one sample to another. A high content of inorganic material has also been found in EMA but is not due to high sulphate or phosphate levels **(29).**

Differential diagnosis of syringoma:

Apocrine hidrocystomas:

They commonly occur as solitary translucent papules or nodules with fluctuant consistency, usually located at lateral canthus of the eye. Their size differs from a few millimeters to around 1.5 cm **(30)**.

Disorders with skin-colored to brown papules:

This category comprises the disorders that as well present with skin-colored to known papules as Darier disease, Hailey-Hailey disease, Fox-Fordyce disease, verruca plana, keratosis pilaris, pseudoxanthoma elasticum, xanthoma, steatocystoma multiplex, eruptive vellus hair cysts, multiple familial trichoepithelioma, secondary syphilis, basal cell naevus syndrome. Moreover drugs eruption should be ruled out **(31)**.

Fox-Fordyce disease:

The lesions of this disease are small infundibulo-centric papules that may have a yellow color and central keratotic plug usually located in the axilla **(32)**.

Xanthoma:

It is a deposition of yellowish cholesterol rich substance in tendons or other body parts in various states of the disease. They are cutaneous manifestations of lipidosis in which there is a gathering of lipids in large foam cells inside the skin **(33)**.

Pseudoxanthoma elasticum:

It is a genetic disease that is characterized by fragmentation and mineralization of elastic fibers in some tissues. The most prevalent problems are in the skin, eyes and blood vessels in the form of premature atherosclerosis **(34)**.

Steatocystoma multiplex:

It is a benign congenital autosomal dominant condition that result in multiple cysts on a person's body. It is also called "sebocytomatosis" or "epidermal polycystic disease" **(35)**.

Eruptive vellus hair cysts:

They are small lesions that arise usually in the chest, abdomen and extremities with a crusted surface. Eruptive vellus hair cysts can be inherited as an autosomal dominant trait or occur randomly. This condition affects males and females evently **(35)**.

Keratosis pilaris:

It is an autosomal dominant, genetic follicular condition that is manifested by the presence of rough bumps on the skin. It usually appears on the back and outer sides of the upper arms but can also occur on the lower arms, thighs, hands, buttocks or any part of the body except glabrous skin like the palms and soles of feet. Lesions less likely to appear on the face and may be mistaken for acne **(36)**.

References

1. *Lee JH, Chang JY, Lee KH (2007):Syringoma: a clinicopathologic and immunohistologic study and results of treatment. Yonsei Med J;48(1):35-40.*
2. *Seo HM, Choi JY, Min J, Kim WS (2016): Carbon dioxide laser combined with botulinum toxin A for patients with periorbital syringomas. J cosmet Laser Ther; 18 (3): 149-53.*
3. *Kaposi M.(1874): Hebra diseases of the skin. Lymphangioma Tuberosum Multiplex. London, the New Sydendham Society. ;3 :386.*

4. *Heo YS, Oh TS, Oh CH, Song HJ (2010): A case of axillar syringoma. Ann Dermatol; 22 (1): 85-87.*
5. *Avhad G, Chuge P, Jerajani HR (2015): Generalized eruptive syringoma. Indian J Dermatol; 60 (2): 214.*
6. *Schepis C, Torre V, Siraguna M, Albiero F, Cicciarello R, Guglarti ME, et al. (2001): Eruptive syringomas with calcium deposits in a young woman with Down's syndrome. Dermatol; 203 (4): 345-7.*
7. *Verma SB (2011): An unusual case of eruptive syringomas presenting as itchy symmetrical lesions on both forearms in a patient of hyperkeratotic eczema. Indian Dermatol; 2 (2): 104.*
8. *Karatzi C, Stefanidou M, Chaniotis V, Evangelou G, Krueger-Krasagaakis S, Krasagakis K (2018): Treatment of giant vulvar syringoma with topical adelmidrol: The role of mast cells. Australs J Dermatol; 2 (2): 10-1.*
9. *Huang YH, Chuang YH, Kuo TT, Yang LC, Hong HS (2003): Vulvar syringoma: A clinicopathologic and immunologic study of 18 patients and results of treatment. J Am Acad Dermatol; 48 (5): 735-9.*
10. *Timpanidis PC, Lakkani SR, Groves RW (2003): Progesterone receptor-positive eruptive syringoma associated with diabetes. J Am AcadDermatol; 48 (5): 103-4.*
11. *Lei H, Wang Z, Ma X, Zhang Z, Feng Y and Zheng Y (2023): Eruptive syringomas: summary of ninety cases and a brief literature review. J Cosmet Dermatol, 22(3);1128-1133.*
12. *Kumar YHK, Keethi S (2014): Eruptive syringoma-A great mimicker:an uncommon presentation in males. In J Health Allied Sciences; 3 (4): 270.*
13. *Metze D, Wigbels B, Hildebrand A (2001): Familial syringoma: a rare clinical variant. Hautarzt; 52 (11): 1045-8.*
14. *Butterworth T, Strean LP, Beerman H, Wood MG (1964):Syringoma and mongolism. Arch Dermatol; 90 (5): 483-7.*
15. *Headington JT, Koski J, Murpjy PJ (1972): Clear cell glycogenosis in multiple syringomas. Description and enzyme histochemistry. Arch Dermatol; 106 (3): 353-6.*
16. *Saitoh A, Ohtake N, Fukuda S, Tamaki K (1993): Clear cells of eccrine glands in a patient with clear cell syringoma associated with diabetes mellitus. Am J Dermatopathol; 15 (2): 166-8.*
17. *Furue M, Hori Y and Nakabayashi Y (1984): Clear-cell syringoma: association with diabetes mellitus. The American journal of dermatopathology, 6(2):131-138.*
18. *Ohnishi T, Watanabe S (1997):Immunohistochemical analysis of keratin expression in clear cell syringoma: A comparative study with conventional syringoma. J CutanPathol; 24 (6): 370-6.*
19. *Carneiro SJ,Gardner HL,Knox JM (1971): Syringoma Of the vulva. Arch dermatol; 103(5):494-6*
20. *Choi HJ, Lee YJ, Park SH, Kim HU, Yun SK, Ibm CW (2005): A case vulvar syringoma with pruritus. Korean J Dermatol; 43 (2): 291-3.*
21. *Berk DR, Bayliss SJ (2008):Milia: a review and classification. J Am Acad Dermatol; 59 (6): 1050-63.*
22. *Garci C, Krunic AL, Grichnik J, Viehman G, Clark RE (1997): Multiple acral syringomata with uniform involvement of the hands and feet. Cutis; 59 (4): 213-4.*
23. *Dutra Rezende H, Madia ACT, Elias BM, Peraro TDF and Mattos Dinato SL (2022): Comment on: eruptive syringoma–two cases with dermoscopic features. Skin appendage disord; 8(1):81-82.*
24. *Botsali A, Caliskan E, Coskun A and Tunca M (2020): Eruptive syringoma: two cases with dermoscopic features. Skin appendage disorders; 6(5):319-322.*
25. *Ghanadan A, Khosravi M (2013): Cutaneous syringoma: A clinicopathologic study of 34 new cases and review of the literature. Indian J Dermatol; 58 (4): 326.*
26. *Kim BC, Park EJ, Kwon IH, Cho HJ, Park HR, Kim KH and Kim KJ (2012): An immunohistochemical study of the origin of the solid strand in syringoma, using carcinoembryonic antigen, epithelial membrane antigen, and cytokeratin 5. Int J Dermatol; 51(7):817-822.*
27. *Obaidat NA, Alsaad KO, Ghazarian D (2007): Skin adnexal neoplasms- part 2: An approach to tumours of cutaneous sweat glands. J ClinPathol; 60 (2): 145-59.*
28. *Moll R, Moll I and Franke WW (1984): Differences of expression of cytokeratin polypeptides in various epithelial skin tumors. Arch dermatol res; 276:349-363.*
29. *Ormerod MG, Steele K, Westwood JH and Mazzini MN (1983) Epithelial membrane antigen: partial purification, assay and properties; BJC, 48(4):533-541.*
30. *Alessi E, Gianotti R, Coggi A (1997): Multiple apocrine hidrocystomas of the eyelids. Br J Dermatol; 137 (4): 642-5.*
31. *Frazier CC, Camacho AP, Cockerell CJ (2001):The treatment of eruptive syringomas in an African American patient with a combination of trichloroacetic acid and CO2 laser destruction. Dermatol Surg;27(5):489-92.*
32. *Boer A (2004): Patterns histopathologic of fox-fordyce disease. Am J Dermatopathol; 26 (6): 482-92.*
33. *Zak A, Zeman M, Slaby A, Vecka M (2014):Xanthomas: Clinical and pathophysiological relations, Biomed Pap Med Fac Univ Palacky Olomouc; 158 (2): 181-8.*
34. *Chassaing N, Martin L, Calvas P, Lebert M, Hovnanina A (2005):Pseudoxanthomaelasticum: A clinical, pathophysiological and genetic update including 11 novel ABCC6 mutaations. J Med Cancer; 42 (12): 881-92.*
35. *Alsabbagh MM (2016): Steatocystoma multiplex: A review. J Dermatol Surg; 20 (2): 91-9.*
36. *Hwang S, Schwartz RA (2008): Keratosis pilaris: A common follicular hyperkeratosis. Cutis; 82 (3): 177-80.*