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Review Article

Literature Review of Sebaceous and Non-Sebaceous Lymphadenoma

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Abstract

Lymphadenoma of the salivary gland is a rare form of tumor that can be branched into Sebaceous Lymphadenoma (SLA) and Non-Sebaceous Lymphadenoma (NSLA). It is painless, hyperdense, shiny yellowish/brownish unicystic or multicystic mass which is encapsulated and well defined having lymphocytic and/or lymphoid follicles background present with or without sebaceous differentiation. Both SLA and NSLA are predominantly located in parotids with occasional case appearing in minor salivary glands and has <100 and <50 reported cases respectively in English literature. We have attempted to compile reported case studies on SLA and NSLA and tried to make analysis on the basis of findings. Our analysis revealed that both SLA and NSLA are often non-malignant in nature but feature of malignancy cannot be completely ruled out. Data also found that SLA and NSLA has a significant gender bias towards males but NSLA is more likely to appear at an early age as compared to SLA which often emerge after the 5th decade of life. Further, differential diagnosis should be considered to distinguish SLA and NSLA from Warthin's tumor, pleomorphic adenoma, mucoepidermoid carcinoma, cystadenoma, lymphoepithelial cysts, myoepithelial sialadenitis, malignant lymphoma and metastatic adenocarcinoma of lymph node. This review discusses various techniques used in the past studies that can be helpful in making differential diagnosis.

Keywords: Lymphadenoma; Sebaceous lymphadenoma; Non-sebaceous lymphadenoma; Differential diagnosis

Introduction

Lymphadenoma of the salivary glands is an infrequent tumor [1], which can be branched into Sebaceous Lymphadenoma (SLA) and Non-Sebaceous Lymphadenoma (NSLA) depending upon whether it involves the sebaceous cell differentiation or not [2]. The term 'Lymphadenoma' was previously being used for Hodgkin's disease [3-7], but later its etymology modified to denote a different state. The glandular salivary glands are composed of two types of cells comprising of luminal and abluminal cells. The luminal cells are composed of secretory acini and intercalated ducts which are surrounded by myoepithelial cells whereas the remaining portion is sustained by basal cells. The salivary glands tumors can be monophasic comprising either of luminal cells or abluminal cells type. Alternatively, they can be biphasic including both luminal and abluminal differentiation. Some rare salivary glands tumors including lymphadenoma manifest additional element of sebaceous or non-sebaceous differentiation like SLA or NSLA [8,9]. The prominent markers of luminal cells are low-molecular-weight Cytokeratin (CK) for example CAM 5.2, Epithelial Membrane Antigen (EMA) and CD117/c-kit, while abluminal cells are positive for CD10 and p63 [9,10]. Both SLA and NSLA are included in the WHO's 2005 classification which classified the salivary glands tumors into epithelial and mesenchymal tumors that can then be classified into benign and/or malignant type [11].

Lymph node tumors are generally asymptomatic, and mainly occur without family history or gender preference. Although commonly lymphadenoma don't complain about facial nerve dysfunction or any other aggravated feelings, some previous studies have reported paralysis of larynx or pharynx in patients with SLA or NSLA [12].

Sebaceous Lymphadenoma (SLA)

The presence of sebaceous glands in interlobular ducts of parotid glands were confirmed in 1946 by Hart et al. [13] and later by others [14]. Presence of sebaceous glands in normal parotid were also confirmed latter by L Meza-Chavez with parotid tumors mass [15]. Relatively older literary mentions can also be found without much elaboration [16,17]. Whereas great majority of the cases of SLA are reported in parotid salivary gland, there are few exceptions where minor salivary glands are found involved [18-20]. Some rare and relatively older instances also reported lymphadenoma in bladder [21] and larynx [22], Ileal Side of Bauhin's Valve and jejunum in literature from other languages [23,24] but their endorsements in English language literature are missing altogether probably because its etymology was related with Hodgkin's disease previously. Interestingly Annikka Weissferdt et al. pointed two medical cases where lymphadenoma was not developed in parotid glands or salivary glands. To best of our knowledge this was the first clinical report highlighting the presence of lymphadenoma in thymus [25]. Lymphadenoma with sebaceous differentiation was first introduced by Rawson and Horn in 1950 as tumor within the parotid salivary gland comprising of sebaceous glands and lymphoid tissue [26].

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It was followed by a 'sebaceous gland like tumor' case reported in USA by Foote and Frazell out of 766 parotid tumors patients [27]. But this case presented a mature mass of sebaceous cells without the participation of lymphoid tissues rightly called as 'sebaceous adenoma'. It can be noticed that discovery of sebaceous gland inside parotids aided the true clinical diagnosis of SLA soon after.

SLA are part of WHO disease classification published in 2005. It defined it as encapsulated, well defined mass of varying sizes with lymphocytic and/or lymphoid follicles background [11]. The clinical manifestation of SLA is usually presented as painless solid monocystic or multicystic mass with size most often ranging between approximately 1.3 to 6.0 cm, and diagnosed by immunohistochemistry in general. It usually occurs in middle-aged and elderly people, and the lesions are mostly located in part of the abundant glands such as parotid and submandibular glands, and a small part is located in the thymus. Large three dimensional bands of non-keratinized squamous cells with oval nuclei comprising of evenly dispersed chromatin with limited to modest dense cytoplasm were seen with "stream of fish" arrangement [28]. Rare granulomas and cystic contents (degenerated cells, inflammatory cells, macrophages, and abundant granular debris/proteinaceous material) were also observed. A case study put forward by Golsa Shekarkhar and comrades suggested shiny brownish well encapsulated mass containing ductal epithelial components with squamous and sebaceous differentiation and multiple lymphoid follicles. The solid, hyperdense mass was located on the posteromedial side of left parotid gland without the presence of oncocytes or fat tissues which is generally suggestive of benign arrangement [29]. Physical examination of SLA often reveal a stable, fixed and non-tender mass without any clear signs but an isolated case of 87 years old revealed that 'reddish livid plaques at the left cheek and the left neck' are seen in sebaceous adenocarcinoma [30].

Although number of cases reported in the literature establish lymphadenoma as a rare disease, but indistinct diagnosis with other related adenomas like Warthin's tumor, pleomorphic adenoma, mucoepidermoid carcinoma, cystadenoma, lymphoepithelial cysts, myoepithelial sialadenitis, malignant lymphoma and metastatic adenocarcinoma of lymph node seems to be partly responsible. For instance, Mcgavran et al. testified two distinct cases at Washington University School of Medicine, St. Louis and termed them neoplasms of the parotid salivary gland comprising solely of sebaceous glands and lymphoid tissue mass. Authors warned that this 'sebaceous lymphadenoma' is clinically different from papillary cystadenoma lymphoma as latter has germinal centers in lymphoid tissues found to be absent in SLA. It is also different from mucoepidermoid carcinoma as latter is devoid of any lymphoid tissue involvements [31]. SLA can also be differentiated from lymphoepithelial sialadenitis as latter has more proliferative epithelial constituents [11]. This diagnostic problem was also appreciated by Musthyala and colleagues who cited the lymphadenoma case of a 74 years old with a mass in the parotid gland. The details revealed a greyish/whitish well defined mass with anastomosing islands of epithelial cells with a dense lymphoid stromal background [32]. Recently Vazmitsel and colleagues provided a guideline for the diagnostic differentiation of SLA from other related neoplasm as it contains a conspicuous lymphoid background and epithelial cells with a vacuolated cytoplasm [33]. In 2002 J Ma highlighted three Lymphadenoma cases of salivary glands with age ranging from 13 to 57 years having well demarcated mass with anastomosing trabeculae containing conspicuous lymphoid stroma devoid of sinuses [34]. Author also hinted at the misleading diagnosis problem presented by this rare disorder. Although there is a common feature of recognizable diagnostic difficulty among various studies but WHO report published in 2005 put differential diagnosis of SLA as the one which shows deficient mitotic activity, lacking invasive growth, obvious ductal differentiation and absence of Epstein–Barr Virus (EBV) association [11]. It is plausible to argue that SLA can pose a diagnostic confusion with other related parotid tumors, hence careful histopathological analysis along with other techniques should be consider before reaching any definite conclusion.

Various scientific techniques are used to diagnose SLA, but Fine Needle Aspiration (FNA), ultrasound, Magnetic Resonance Imaging (MRI) and histopathological methods are found prominent in literature. Boyle and Meschter stated a solitary 75-year-old male case report which was confirmed as SLA through FNA. Report stressed that FNA provides a sufficient mean to diagnose SLA [35]. However, Hayashi et al. reiterated the need to be cautious, while citing two SLA cases, in making diagnosis with FNA [36]. A variant of this technique was introduced by Banich et al. who used Fine Needle Aspiration Biopsy (FNAB). This report advised the use of FNAB before the use of definitive biopsy which may ultimately be required for detailed diagnosis [37]. Ultrasound and MRI are also used to know the features of SLA [38]. Another study on 82 years old with SLA confirmed through incisional biopsy reported its successful treatment after superficial right parotidectomy with face nerve spared [39].

Less than 100 case reports of SLA are recorded in English literature to the best of our knowledge which provided valuable information about this rare disorder. Gnepp and brannon offered the case history of 21 patients who were diagnose with primary sebaceous tumors of salivary glands. Among them five were diagnose with sebaceous adenomas, nine with SLA, five with sebaceous carcinomas and two with sebaceous lymph adenocarcinomas. 81% of the tumors were found in parotid gland while rest were located in submandibular gland, the minor salivary glands of buccal mucosa and ectopic salivary gland tissue. Authors found greater tendency of SLA's in males [40]. Seethala et al. recorded 31 patient's data, among which 21 were diagnosed with SLA while 10 were suffering from NSLA. The conclusion is that compared with SLA, NSLA prefers females and has more chances to occur outside the parotid gland. Compromised immune system can further the chances of SLA and NSLA to occur [41]. One original case of 62 years old male with total parotidectomy showed infiltration of Myeloid Sarcoma (MS) into SLA along with simultaneous bone marrow involvement. Authors concluded that majority of the cases suffering from MS show salivary glands invasion that can be manifested by bone marrow participation [42]. An usual case of bilateral parotid gland tumor with mixed features on one side and SLA on other side was also seen in 65 years old women [43]. The case history of 58 years old male and 77 years old female showed positive results for cytokeratin 8, cytokeratin 5/6, and adipophilin in the sebaceous component while B- and T-cell markers were found positive in the lymphoid component [25]. SLA cells also presented clonal chromosomal deviations [44]. From the various cases reported in the literature, it can be noted that compared with other sexes, men have a slightly higher risk of salivary gland SLA, and most

cases appear in the late stage (after 6th decade of life). Slight gender predilection can be attributed to robust presence of sebaceous glands in males [45]. In addition, unique cases of cystic SLA of the parotid gland [46-50] and other typical case reports of SLA are also reported elsewhere in literature [51-68].

Although SLA mass is primarily composed of sebaceous and lymphoid component but there is evidence of fat section as well. For example, Tschen and companions performed thin-layer chromatography to reveal lipid analysis in SLA. Study found no difference in the type or morphology of lipids between SLA and cutaneous sebaceous glands [69]. A study used sections for Computer Tomography (CT) images and found inconsistent mass with dispersed fat density zones. In the same study magnetic resonance (MR) images showed a mass with fat rich parts and an enhanced capsule [70].

It remains largely unknown whether any kind of comorbidity increases the risk of developing SLA. However, Cowden Syndrome (CS) known as an uncommon autosomal dominant genodermatosis, has been reported along SLA in at least two case reports [71,72]. Co-existence of lymphadenoma with tuberculosis is also reported in the literature [73]. A well-documented case in which patient complained about chest disturbances, nausea, vomiting, weight loss and depression was admitted under the suspicion of tuberculosis, which showed the 'characteristics of lymphadenoma' after the surgical removal [74]. Both of these two case reports belong to 1920's era which could be a result of mistaken differential diagnosis at that time but lymphadenoma should be suspected in tuberculosis patient where it is required.

The malignancy is a rare occurring in an infrequent SLA. However, a group of scientist narrated the synchronous manifestation of SLA with squamous cell carcinoma [75]. Likewise, Mayorga and companion was first to report the presence of synchronous ipsilateral SLA and an acinar cell adenocarcinoma [76]. Furthermore, the occurrence of synchronous ipsilateral SLA with membranous cell adenoma of the Parotid [77], breast cancer [78] and Warthin tumor are also reported [79]. In 2003 Croitoru et al. presented only fourth case of sebaceous lymphatic adenocarcinoma and alerted that malignancy should be considered in SLA cases despite of its rare occurrences [80]. Similarly, another case of 36 years old male was diagnosed with typical SLA with transition to a sebaceous adenocarcinoma [81]. A rare report highlighted the presence of Sebaceous 'lesion masquerading as a metastatic node' in a male patient going through mixed testicular germ cell tumor chemotherapy [82]. Henrik Hellquist and colleagues also described the diagnostic difficulty related to all type of malignant salivary gland tumors and found no biomarker which can be used for predicting recurrence or potential malignant development [83]. These all evidences suggest that despite of SLA's rarity and its benign nature, malignancy cannot be ruled out and may be consider in post-parotidectomy events.

The occurrence of SLA among newborns and children is rarest of the rare event as compared to adults [84, 85]. One such instance is reported way back in 1910 by R. Miller who showed lymphadenoma in 25 month old male patient [86]. One of the youngest case suffering from SLA is presented by Rawlinson and colleagues in 2010 in which 2×2 mass was found in left submandibular of a 13 years old female. Researcher noted biphasic mass with both of the lymph nodes found unremarkable. It was also stated that sebaceous differentiation is likely dependent on the hormonal secretion which is the reason for SLA rarity in children and teenagers [87].

Non-sebaceous Lymphadenoma (NSLA)

NSLA is also rare like SLA accounting for less than 50 cases in English scientific literature till now [88], and most of these cases are women. These cases are predominantly reported in parotid gland with fewer submandibular and sublingual gland occurrences. Recently however, there is one case reported where NSLA was found in lacrimal glands [89]. Additionally, another group of scientists narrated NSLA case with left submandibular gland tumor having atypical findings with marked lymphoepithelial differentiation which is usually absent in such tumors [90]. It is interesting to notice that majority of the cases do not show recurrence postoperatively or malignant transformation unlike other tumoral masses.

NSLA was characterize as well confined solid squamous islands restricted under dense lymphoid stroma and epithelial cells were devoid of any sebaceous differentiation [91]. Shobha Castelino-Prabhu reported NSLA as hard, movable benign left parotid mass with a uniform population of cohesive basaloid-type cells linked with scant myxoid stroma [92]. There is at least one reported case where chondrocyte differentiation was observed along with the presence of luminal and myoepithelial cells in NSLA [93].

A china-based study concluded in 2014 presented 10 cases of lymphadenoma reported between 1996 and 2012. The data indicated relation to parotid glands in all cases and displayed 70/30 ratio of cases in favor of NSLA. Thorough surgical resection was determined as first choice therapy [94]. Recently Hiroaki Yamanaka et al. reported a unique case of 65-years Japanese female suffering from painless left parotid mass with a history of biliary cholangitis for last 08 years. Authors used Gallium-67 (Ga67) and 99mTc pertechnetate scintigraphy for differential diagnosis and found mild accumulation of the latter after oral stimulation with ascorbic acid and calcium pantothenate combination. It was concluded that positive technetium-99m (99mTc) can be used as a mean to differentiate NSLA from other clinical overlapping states [95].

The development of malignancy is not the feature of NSLA and its non-malignant nature is considered as the cardinal signal for diagnosis. But a recently published case report of 54 years old female patient with right preauricular mass showed clear signs of malignancy after complete parotidectomy was performed [96]. An unusual case of NSLA of the parotid gland with the manifestation of serous acinic cell differentiation was presented by Ishii et al. The mass was measured as having encapsulated frame with the size of 13 × 9 × 9 mm. Authors warned that there is a probability of epithelial cells differentiation into serous acinic cell and hence this feature should also be considered during the differential diagnosis of NSLA [97]. Another case report of 58-year-old female showed tumor mass with the presence of both luminal and myoepithelial cells. Researchers claimed that the tumor was DNA diploid [98]. Daisuke Mori et al. reported two cases of NSLA containing cysts which were lined with luminal and abluminal cells. Abluminal cells manifested metaplasia or hyperplasia which left researchers undecided whether it was true neoplasia or an indication of a nonneoplastic reactive process [99]. Likewise, these findings are confirmed by other report showing

luminal and abluminal differentiation and non-cyclic tumor cells with normal karyotype [100]. Mitsuharu Aga and comrades first time described association between Immunoglobulin G4 (IgG4) and Warthin's tumors where IgG4 manifested raised penetration in 71 years old patient [101]. Other research group also endorsed this finding [102]. In an extension, a Korean group led by Jiyoon Kim et al. found similar kind of IgG4 plasma cells involved in the NSLA of the salivary gland [103]. The presence of IgG cells are in NSLA is also confirmed previously [104]. Like SLA, the malignancy in NSLA is not a usual occurrence but should be suspected in the light of few above mentioned cases.

Number of markers are identified that can differentially recognize NSLA and help in diagnosis. For instance, Francesca Angiero et al. found NSLA positive for AE1/3, CKA, P63, BclII, CD3, CD79a and MYC. Authors pointed MYC and PRDM1 as the key transcription factors in NSLA neoplasm [105]. Keratin (CK) profile of Lymphadenoma revealed presence of CKs 7, 8/18, and 19, while CK14 was only expressed isolated group cells. Though CK10/13 was negative [106]. Weiler and comrades noted robust expression of CK5/6, CK14, and p63 in basaloid or lymphoepithelial differentiated cells and areas with ductal differentiation manifested positivity for CK18/CK7 and CK5/6/CK14/p63 in luminal and basal cell layers [107].

Conclusion

Lymphadenoma of the salivary gland can be divided into SLA and NSLA depending upon the participation of sebaceous gland. We found <100 cases of SLA and <50 cases of NSLA in our search (Predominantly English literature). It was noticed that both SLA and NSLA are more common in males but NSLA involves greater percentage of female incidences (approx. 37.5%) as compared to SLA (<13%). It was also observed that NSLA is more likely to appear in younger age as compared to SLA which is more likely to emerge in or after fifth decade of life. Data shows that Both SLA and NSLA greatly occur in parotid gland but occasional cases can be found in minor salivary glands as well.

Most of the SLA and NSLA tumors found were non-malignant but there are traces of malignancy observed in an occasional case. It was noted that both SLA and NSLA present a significant diagnostic challenge which require careful examination and reassurance. Though current literature on SLA and NSLA is very limited and spread over decades but its careful analysis can help differentiate among related states.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships.

Author Contributions

All authors contributed to the writing and editing of the manuscript and approved the final draft of the manuscript.

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Data Availability Statement

All datasets generated for this study are included in the manuscript/supplementary files.

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