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The Coral Crunch- Amyloidoma

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Preface

Amyloidoma is an exceptional, progressive disorder constituted by a plethora of conditions with characteristic accumulation of significant quantities of amyloid within soft tissues. Amyloidoma is additionally nomenclated as tumoural amyloidosis or nodular amyloid wherein insulin-derived amyloidoma is referred to as insulin ball. Amyloid nodules may be associated with systemic amyloidosis. Amyloid is a protein polymer configured with identical monomeric protein units. Pathological variety of amyloid is articulated from misfolded proteins. In excess > of twenty-three subtypes of protein can configure amyloid fibres in vivo. Extra-cellular or intra-cellular deposition of amyloid can modify normal organ function [1]. Amyloidosis is categorized into systemic and localized subtypes. Localized amyloidosis is accompanied by a localized mass effect and demonstrates a superior prognosis. Insulin-derived amyloidosis was initially documented by Storkel et al in 1983 who recognized insulin-amyloid fibrils in diabetic individuals subjected to continuous infusion of porcine insulin for a period of 5 weeks or more [1,2]. **Disease Pathogenesis** Amyloidosis is classified pertaining to cogent clinical and pathological criterion as

a) primary amyloidosis demonstrating an absence of an identifiable cause
b) secondary amyloidosis emerging as a consequence of chronic diseases such as tuberculosis or rheumatoid arthritis
c) amyloidosis associated with multiple myeloma
d) localized amyloidosis which characteristically displays absence of evident systemic incrimination or underlying chronic disease [1]. Contemporary, chemical classification of amyloidosis is contingent to accumulated protein subtype and is characterized as amyloid associated (AA) or amyloid light- chain (AL) amyloidosis. AL amyloidosis ensues with production of aberrant antibodies within the bone marrow which are resistant to denaturation. Aforesaid antibodies configure amyloid and are deposited within soft tissues thereby engendering organ dysfunction [1]. Systemic amyloidosis is denominated by diverse categories of amyloid accumulation

a) amyloid associated (AA) amyloidosis which exhibits precursor serum amyloid A and exemplifies a frequent variant of systemic amyloidosis usually incriminating the spleen, hepatic and renal parenchyma. Diverse rheumatologic disorders (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis), autoimmune disorders (psoriasis, psoriatic arthritis) or haematological malignancies (Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma) are associated with systemic amyloidosis. Previously treated mycobacterial infection or pulmonary tuberculosis and chronic inflammation arising due to repetitive respiratory tract infections may incur AA amyloidosis.
b)Light –chain (AL) amyloidosis is a variant of systemic amyloidosis where clonal immunoglobulin light- chains or light- chain fragments configure the precursor protein. AL amyloidosis commonly implicates cardiac tissue, renal parenchyma, gastrointestinal tract, respiratory tract or peripheral nervous system.
c) Heavy chain (AH) amyloidosis is engendered by accumulation of fibrils

of immunoglobulin heavy chain sequences [3,4]. Amyloidosis can also occur with the deposition of transthyretin or beta-2 microglobulin thereby articulating transthyretin amyloidosis (ATTR) or beta-2 microglobulin amyloidosis (Abeta2M) or associated varieties of systemic amyloidosis. Localized amyloidosis is configured by on site production and accumulation of amyloid substance in diverse tissues and organs. Mature plasma cells secrete abundant quantities of light chain immunoglobulins which misfold with localized deposition [3,4]. Localized amyloidosis or "amyloidoma" represents a true neoplasm rather than a pseudo tumour and may be incurred by plasma cells. Specifically, clonal expansion of singular plasma cell is denominated within localized (AL) amyloidosis. Localized amyloidosis can appear within the urinary bladder, trachea, bronchi, larynx, gastrointestinal tract, orbit, tonsils, lymph nodes and cutaneous surfaces. Localized amyloidosis is frequently and significantly associated with Sjogren's syndrome. Localized amyloidosis of the brain tissue typically engenders Alzheimer's disease [3,4]. Precise aetiology of localized amyloidosis is obscure. As amyloidosis is usually articulated within mucous membranes, prolonged activation of tissue plasma cells due to exposure to environmental antigens is a preliminary step in disease generation. Reactive plasma cells exhibit enhanced production of amyloidogenic immunoglobulin light chains. Transformation of aforesaid immunoglobulin light chains into insoluble fibrils due to activation of tissue macrophages is a key mechanism in articulating the amyloidoma. The hypothesis is validated by presence of several multinucleated giant cells within lesions of localized amyloidosis.

Localized amyloidosis frequently involves larynx within the head and neck, in contrast to incrimination and extensive enlargement of the tongue in systemic amyloidosis with engenderment of "macroglossia". Localized amyloidosis rarely implicates the tongue. Certain foci demonstrate nodules or localized accumulation of amyloid protein [3,4]. **Disease Characteristics** The asymptomatic, nodular tumefaction is usually discerned in adults and elderly population. Commonly incriminated sites are lower extremities, cutaneous surfaces or subcutaneous tissue. The condition is idiopathic or may arise as a consequence of multiple myeloma or plasmacytoid lymphoma or in individuals with chronic inflammation or on long-term dialysis [5]. Contemporary recommendations pertaining to categorization of amyloidosis are

a) Congo red staining is contemplated as the gold standard for detection of amyloid

b) appropriate discernment of amyloid subtype requires adequate microscopic or immune histochemical assessment and singular dependence upon clinical or deoxy ribonucleic acid (DNA) assay may be insufficient

c) immuno-histochemical analysis is to be performed competently and suspicion of amyloidosis requires confirmation with sophisticated techniques [5].

Insulin- derived amyloidosis is commonly discerned in subjects with inadequate glycaemic control with values of glycosylated haemoglobin (HbA1c) between 7.6% to 15.5% and duration of insulin therapy varying from 4 years to 60 years. Insulin-derived amyloidosis is a disorder of enhancing prevalence. Insulin- derived amyloidosis commonly incriminates the abdomen (70%), thigh (15%), upper extremity (13%), breast (1%) or inguinal lymph nodes (1%). Insulin-derived amyloidoma is discerned in 3.5% of individuals subjected to aspiration of abdominal adipose tissue in order to exclude systemic amyloidosis. Following pertinent insulin therapy, around 34% of insulin is absorbed if injected into the site of amyloidoma and hyperglycaemia may ensue [3].

Mechanism of metamorphosis of insulin into amyloid fibrils is inadequately posited and multiple pathways exist. Disassociation of insulin hexamers and dimers into monomeric forms is a predominant step as configuration of fibrils is rapid where the monomer is a dominant species. Also, occurrence of covalent dimers prohibit the articulation of fibrils. Additionally, A and B chains of insulin molecule are amyloidogenic. Thus, localized, iatrogenic, insulin-induced amyloidoma is termed as AIns amyloidosis [3]. Primary cutaneous amyloidoma or drug induced amyloidosis can be induced by Enfuviritide, an anti- retroviral agent employed for treating individuals with human immune deficiency virus (HIV) infection. The drug induces accumulation of amyloid (AEnf amyloid) at injection sites, akin to insulin or subcutaneously administered protein and peptide agents [3,5].

Clinical Elucidation Primary cutaneous amyloidosis principally delineates categories such as lichen (papular) amyloidosis with altered keratin, macular amyloidosis with altered keratin and nodular amyloidosis with light chains (AL amyloid). Incrimination of tongue is common in systemic amyloidosis and may be enunciated as a diffuse enlargement, nomenclated as "macroglossia". Localized amyloidosis appears within the head and neck region, predominantly in larynx or trachea [5,6].

Amyloidoma of the tongue is an extremely exceptional representation of localized amyloidoma. Oral variant of localized amyloidosis is effortlessly discerned upon the tongue which is diffusely enlarged as in macroglossia or delineates a nodular deposit. Extensive incrimination of tongue initiates loss of tissue elasticity and the organ may be firm, fissured, ulcerated, occasionally erythematous and painful. Functional impairment appears as interference with speech, chewing and swallowing. Macroglossia is infrequent in amyloid associated (AA) amyloidosis and common with light chain (AL) amyloidosis. Nevertheless, concurrence of variant amyloid accumulation to cogent clinical representation is unsatisfactory and not recommended. Tissue sampling is mandatory for histological confirmation [5,6]. Insulin- derived amyloidosis exhibits a solitary (90%), firm or soft subcutaneous nodule of variable magnitude appearing at the site of insulin injections.

A cogent clinical history, physical features, investigative procedures as magnetic resonance imaging (MRI) of incriminated sites along with histological assessment in combination with Congo red stain can appropriately discern localized, light- chain (AL) or amyloid associated (AA) amyloidosis [5,6]. **Histological Elucidation** On gross examination, a soft, yellowish, non-friable neoplasm of magnitude varying from one centimetre to three centimetres is delineated. Multiple, translucent, soft tissue fragments display a waxy, firm, starch- like consistency [6]. Upon microscopy, extra-cellular or sub-epithelial deposition of an acellular, eosinophilic, homogenous or matrix-like material is discerned.

Accompanying inflammatory infiltrate is sparse and composed of lymphocytes and mature plasma cells [6]. Insulin-derived amyloidosis demonstrates accumulation a dense, eosinophilic, amorphous material within the subcutaneous tissue. Morphologically, well circumscribed aggregates of amyloid are frequently intermingled with small lymphocytes (T lymphocytes) and plasma cells. Amyloidoma can frequently evoke a granulomatous reaction with dissemination of multinucleated giant cells along with foci of calcification and ossification [6,7]. The tumefaction is configured by islands of amorphous, eosinophilic material admixed with mature plasma cells and multinucleated giant cells. Foci of calcification and metaplastic bone are disseminated within the cellular component. Walls of enmeshed vascular articulations are imbued with amyloid substance [6,7]. Amyloid tissue can be discerned with periodic acid Schiff's stain with pre-digestion with diastase (PASD+). Congo red stain delineates sub-epithelial deposits of reddish, homogenous substance which demonstrate an apple- green birefringence under polarized light. Birefringence persists following pre-treatment with potassium permanganate in primary, light chain amyloidosis (AL) [6,7]. Ultrastructural examination depicts accumulated amyloid fibrils [6].

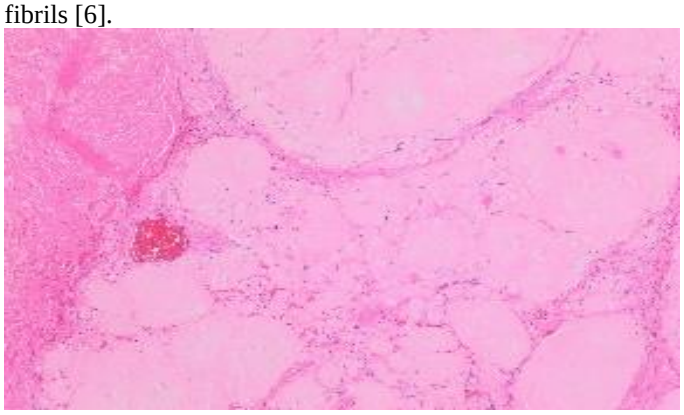

Figure 1. Amyloidoma of trigeminal nerve displaying nodules of acellular, amorphous, eosinophilic material with circumscribing collagen [10].

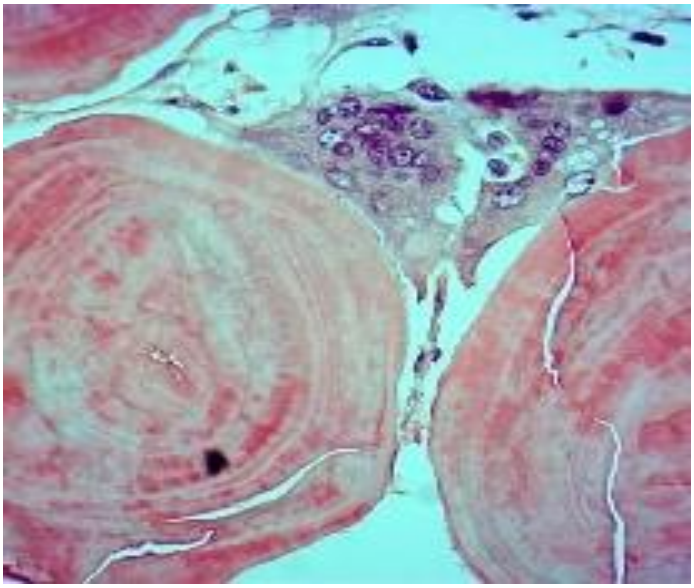

Figure 2. Amyloidoma of pulmonary parenchyma depicting globules of abundant, amorphous, eosinophilic amyloid interspersed with multinucleated giant cells [11].

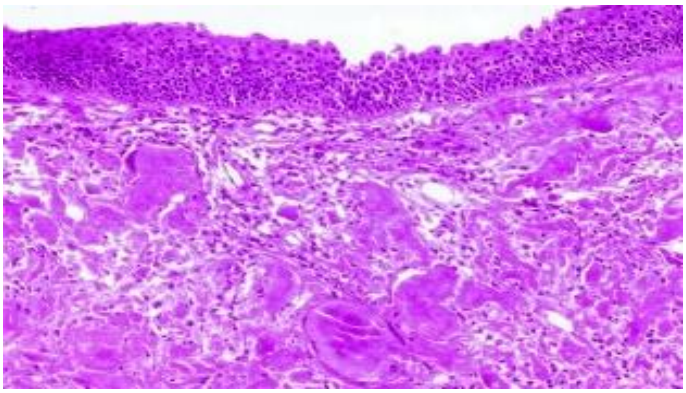

Figure 3. Amyloidoma of larynx exemplifying aggregates of amorphous, eosinophilic substance superimposed by pseudostratified columnar epithelium [12].

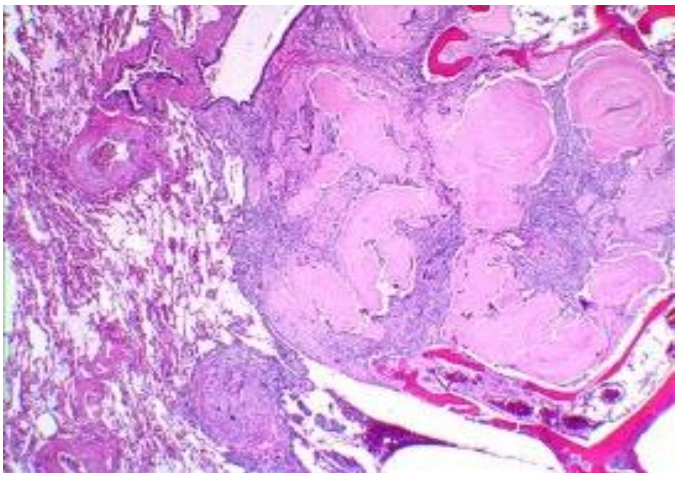

Figure 4. Amyloidoma of soft tissue delineating accumulation of eosinophilic, acellular amyloid material intermixed with inflammatory exudate of plasma cells and lymphocytes [13].

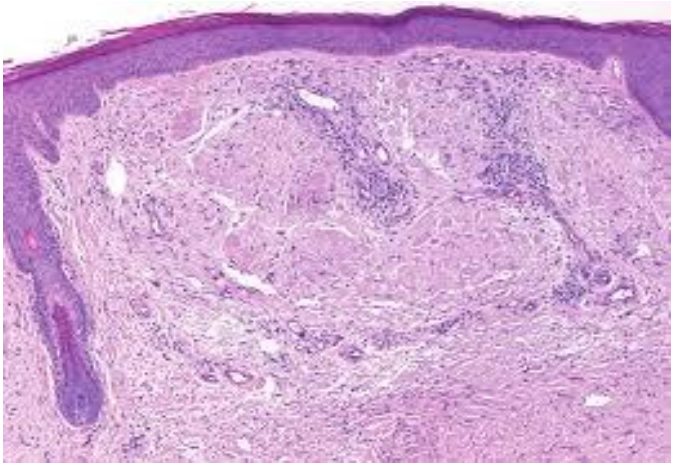

Figure 5. Amyloidoma of cutaneous surface with nodular deposit of acellular, amorphous, eosinophilic substance intermixed with mature lymphocytes and collagen fibres [14].

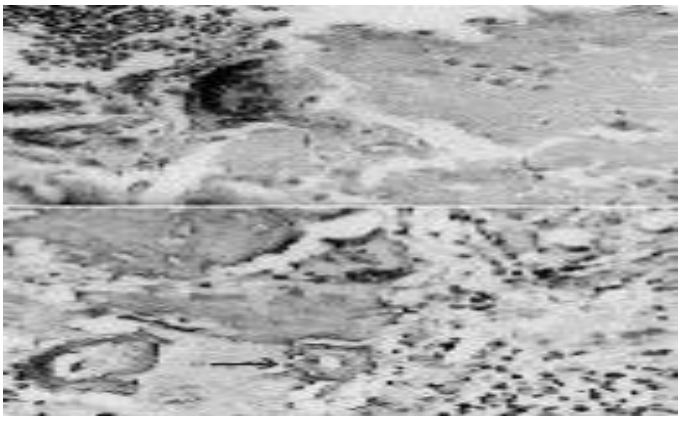

Figure 6. Amyloidoma of the thoracic activity enunciating acellular deposits of eosinophilic material, multinucleated giant cells, lymphocytes and mature plasma cells [15].

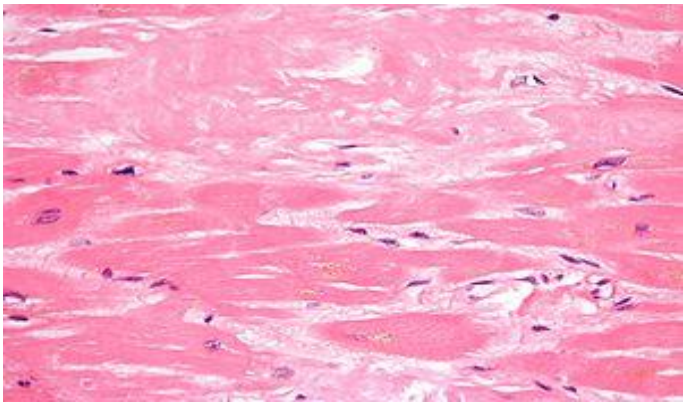

Figure 7. Amyloidoma of the cardiac muscle delineating localized accumulation of acellular, eosinophilic amyloid substance and disseminated lymphocytes [16].

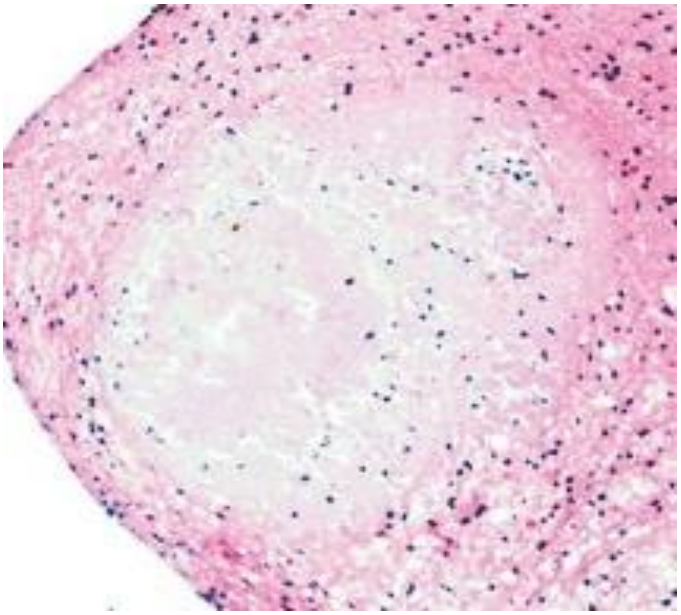

Figure 8. Amyloidoma of the brain depicting localized accumulation of acellular, eosinophilic amyloid material interspersed with chronic inflammatory cells as lymphocytes and plasma cells [17].

Immune Histochemical Elucidation Amyloid staining with Congo red demonstrates a glassy, salmon or pink, amorphous, congophilic material which depicts an apple- green birefringence under polarized microscopy. The neoplasm is immune reactive to CD20, thereby indicating a B lymphocyte origin [6]. In insulin- derived amyloidosis accumulated amyloid is immune reactive to anti-insulin antibodies. The nodule is immune reactive to insulin and demonstrates darkly stained, intense deposits of insulin which confirms insulin derived amyloid [3]. Plasma cells depict a clonal restriction with exemplification of either kappa or lambda light chains. Immune reactivity to kappa or lambda light chains may be adopted in order to confirm a clonal disorder as light chain amyloidosis (AL). Occurrence of amyloid A protein confirms amyloid associated (AA) amyloidosis. However, aforesaid evaluation is imprecise and nonspecific [7,8].
Differential Diagnosis Amyloidoma mandates a segregation from neoplasms such as primary pulmonary lymphoma with amyloid production. An estimated beneath <1% of pulmonary lymphomas delineate amyloid deposits. Generally, individuals exceeding 70 years are incriminated. Subjects with marginal zone or small lymphocytic lymphoma/ chronic lymphatic leukaemia (SLL/ CLL) frequently denominate lymphatic tracking or reactive lymphoid follicles along with evenly disseminated, mature, small lymphocytes within the nodule in combination with pleural infiltration, features which are contemplated as specific for pulmonary lymphoma [7,8]. Hyalinising granuloma is accompanied by history of exposure to fungal agents such as Histoplasma or Mycobacterium tuberculosis. Collagen contained within the lesion may not stain with Congo red [7,8]. Insulin-derived amyloidoma appearing at the site of insulin injection requires a segregation from lipo-hypertrophy, a condition with simulates clinical symptoms of insulin- induced amyloidosis. Clinical distinction may not be possible although insulin lesions are firm in consistency. Individuals with lipo-hypertrophy demonstrate a declining insulin efficacy. In contrast to insulin-induced amyloidosis, magnitude of focal insulin-associated lipo-

hypertrophy decimates with discontinuation of insulin injections [7,8].

Investigative Assay Implicated individuals can be subjected to plain radiography of the chest, echocardiography, N Terminal - pro-brain natriuretic peptide, hepatic fibro-scan, routine haematological and biochemical parameters, immunoelectrophoresis and assessment of adjunctive conditions requiring differentiation [4,5]. Tumour nodule can be discerned upon plain X-ray although evidence of systemic disease is absent [8]. Clinical suspicion of amyloidosis mandates adequate histological confirmation. Cogent tissue specimens can be obtained from sites incriminated with localized amyloidosis and competent microscopy is sufficient to establish the disease. Upon staining with haematoxylin and eosin, amyloid appears as a homogenous, eosinophilic, amorphous substance. Subsequent Congo red staining with polarized light reveals an apple- green birefringence. With confirmation of presence of amyloidosis, the subtype requires categorization which is achieved by immunoelectrophoresis of serum or urine. Aforesaid procedure is also adopted to detect a clonal disorder. Cogent investigations are mandated to exclude factors contributing to systemic amyloidosis [8,9]. Ultrasonography (US) can appropriately define breast amyloidoma and is beneficial in accruing guided tissue samples. Ultrasound can suitably denominate the extent of soft tissue incrimination and recommended, pertinent surgical excision [8,9].

Magnetic resonance imaging (MRI) of incriminated sites such as head and neck demonstrates a polypoid tumefaction of variable magnitude protruding into superimposed cutaneous or mucosal surface. Tumour infiltration into adjacent soft tissue is absent [8,9].

Computerized tomography (CT) and magnetic resonance imaging (MRI) may assist the demarcation between insulin-derived amyloidosis and lipo-hypertrophy. Insulin-induced amyloidoma can be adequately discerned with tissue sampling or aspiration in combination with surgical resection of the nodule [8,9].

Therapeutic Options Prognostic outcome of light chain (AL) amyloidosis is contingent to extent of disease. Localized amyloidosis demonstrates an excellent prognosis and progression to systemic amyloidosis is infrequent [9]. On account of superior prognosis, typically the neoplasm may not progress to a lymphoproliferative disorder. Therefore, localized amyloidosis may not mandate systemic therapy [8,9]. Therapeutic management can be supportive or localized. Common treatment strategies are localized surgical extirpation, ablation or clinical observation of disease. Surgical extermination or ablation of amyloidoma is a preferred treatment modality and is appropriately adopted for management of associated clinical manifestations such as patency of airways [8,9].

Surgical extraction of insulin- derived amyloidosis may be accompanied by extrusion of acellular amyloid from the nodule.

Although surgical resection of the neoplasm is an optimal treatment strategy, adequate clinical monitoring can also be efficaciously performed. Clinical follow up for a duration of two years is usually adequate [8,9]. Tumefaction can be eradicated by laser or electrocautery. Suitable adoption of technique of extrusion can induce significant de-bulking and resolution of amyloidoma. Uniform rotation of sites of insulin injection can be advantageously utilized to circumvent development of amyloidoma. Tumour reoccurrence is frequent [8,9].

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