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Editorial

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By Dr David Muscat

Dear colleagues,

At the time of writing this editorial a mass celebrating the life of the late Dr Ethel Vento Zahra is to be held on 7/11/2022 at the Aula Magna Valletta Campus of the University of Malta.

On October 20th at the Palace Hotel Sliema, the DAM in conjunction with our sponsor Chemimart Ltd organised a lecture by Mr Alex Manche, retired Consultant Maxillo Thoracic Surgeon and founder of the cardiac unit at Mater Dei. The lecture was a medico-historical one and was entitled 'Memories of another Life in Surgery.' This was a great success.

The DAM has organised a lecture entitled 'Update on Treatment with Bisphosphonates and Monoclonal Antibodies and their effects on dental treatment.' This lecture is by Professor Andrew Borg and will be held at The Prince of Wales Band Club in Birgu followed by dinner at Del Borgo. This event is being kindly sponsored by Pro Health as well as The Dental Association of Malta. The event is already oversubscribed.

Dr Ann Meli Attard KOL of GC, in conjunction with Cherubino and the DAM is organising a 'GC Injection Moulding Technique Workshop' at Cherubino Ltd in Gzira on Friday 2nd December. The event will most likely be repeated as there was a great demand. Dr Ann Meli Attard completed her Masters in Clinical Dentistry in Prosthodontics with Distinction from Kings College Dental Institute, London in 2019. She was then awarded the Postgraduate diploma in Aesthetic and Restorative Dentistry from the Academy of Dental Excellence in 2021.

In late November the final group of dentists will attend a one week hands on DAM KA1 course in Northern Italy at Zirkonzahn. The dentists attending will write up about a particular topic they learned about and these articles will be printed in the Probe. The course is funded by EUPA.

The DAM is planning to hold further BLS courses next year. These we had stopped due to the Covid outbreak.

Next year the DAM is also planning to hold the second Mediterranean Dental Conference.

The DAM Christmas party will this year be held at Madliena Lodge on 16th December. This year we should have live music.

May I please remind you to pay your subscriptions promptly. The invoices will be sent out after our AGM in late January. The fee is currently 75 euro per dentist. Unfortunately if the invoice is not settled by 1st July there will be an additional late payment fee of 25 euro due to our administrative costs. The members of the DAM committee work completely free of charge and we at least expect members to pay without us having to chase them. Please co-operate. You may even pay by Revolut or internet banking. Please remember to always fill in your name and details clearly so we know who is remitting. If you wish to send a cheque there is a slip in the Probe you can fill in and cut out and send by post.

The cover picture is by Jacqui Agius and depicts an aerial view of Birgu, the church of Saint Lawrence and the Cottonera Marina.

Have a great Christmas!

David

Dr David Muscat B.D.S. (LON)
Editor / Secretary, P.R.O. D.A.M.

Curaprox DAM event sponsored by Chemimart

On Thursday 20th October the DAM organised a lecture by Mr Alex Manche at The Palace Hotel Sliema .

Mr Alex Manche is a retired Cardiothoracic surgeon. He was the founder of the Cardiac Surgery Unit in Malta. He is a former consultant and chairman of Cardiac Services Mater Dei. Mr Manche recently did a Diploma in the History of Medicine at The Worshipful Society of Apothecaries and won a first prize. The event was kindly sponsored by Chemimart.

Mr Manche's prize involves him having to present an Osler Lecture. This lecture was inaugurated in 1967 and is named after Sir William Osler, the great Medical humanist and historian. It is normally given by the student who is deemed to have delivered the best Test Lecture in the History of Medicine Diploma examination. Mr Manche will be giving this lecture on 23/2/2023.

Mr Alex Manche, Dr Noel Manche, Dr David Muscat and Mr Pierre Fava at The successful Curaprox DAM event at The Palace Hotel Sliema on 20/10/2022.

Dr Noel Manche presenting an inscribed Mdina Glass present to Mr Alex Manche obo The Dental Association of Malta after his lecture at the Curaprox event.

Atypical Multiple Myeloma Presenting In The Oral Cavity

A Case Report presented for the Final Examination in Oral Medicine, Surgery, Pathology and Radiology of the MDS degree of the University of Malta.

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ABBREVIATIONS USED

MM	Multiple Myeloma
MGUS	Monoclonal Gammopathy of Undetermined Significance
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
CT	Computed Tomography
ENT	Ear, Nose & Throat
SPE	Serum Protein Electrophoresis
PCR	Polymerase Chain Reaction
EBV	Epstein-Barr Virus
EBUS	Endobronchial Ultrasound
PCTA	Pulmonary Computed Tomography Angiography
NM	Nuclear Medicine
WBC	White Blood Cell
HHV8	Human Herpes Virus 8
Rd	Lenalidomide, Dexamethasone
VRD	Bortezomib, Lenalidomide, Dexamethasone VTD Bortezomib, Thalidomide, Dexamethasone VCD Bortezomib, Cyclophosphamide, Dexamethasone
VDTPACE	Dexamethasone, Bortezomib, Thalidomide, Cisplatin, Etoposide, Cyclophosphamide, Doxorubicin
CRAB	Calcium, Renal Failure, Anaemia, Bone lesions
IMWG	International Myeloma Working Group
NHS	National Health Service

ABSTRACT

Multiple myeloma (MM) is a plasma cell malignancy. Features include anaemia, hypercalcemia, chronic renal failure, amyloid deposition (amyloidosis), infections, and lytic lesions causing bone pain and/or fractures. Multiple myeloma can have a varied presentation. Oral manifestations, mostly clinical swellings and infiltrative masses on imaging, occur in approximately 30% of cases but rarely as the presenting feature. Oral presentation, may be the sole presenting feature or from part of a spectrum of signs and symptoms. This case report describes a patient who was referred to hospital because of a non-resolving swelling in the palate. A diagnosis of MM was based on the histological picture of a high-grade malignancy, the immunohistochemical panel favouring a plasma cell neoplasm, demonstration of a monoclonal band on serum electrophoresis and widespread bone and soft tissue lesions seen on imaging. There was no response to aggressive chemotherapy and unfortunately the patient passed-away two months after diagnosis. The disease in the presented case was not typical of the expected findings in MM cases. The disease presented in the mouth; a rare occurrence in MM.

Furthermore, the patient was relatively asymptomatic, initially hypocalcaemic, had an atypical immunoglobulin pattern, immunohistochemical results were not clear cut and the disease spread was extensive. Atypical disease presentation makes diagnosis challenging, potentially leading to misdiagnosis or to delays in diagnosis. This case report highlights the dentists' duty of thoroughly examining the mouth for suspicious lesions indicative of serious underlying disease. To increase chances of a favourable prognosis, dentists must be attentive to the oral manifestations of MM in order to be able to investigate and refer promptly.

KEYWORDS

Atypical, Multiple Myeloma, Palate, Oral cavity

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INTRODUCTION

Multiple Myeloma (MM) is a multifocal neoplastic proliferation of plasma cells. Although originating in the bone marrow and predominantly involving it, disseminated involvement is frequent and evidence of organ damage is commonplace. This disease has a varied clinical spectrum, ranging from asymptomatic to highly aggressive (Swerdlow et al., 2017).

MM accounts for around 1% of malignant tumours worldwide and 10-15% of haematopoietic neoplasms. Globally, MM results in 20% of haematological malignancy-related mortality. 90% of cases occur in patients over 50-years-old and the disease almost never occurs in children and young adults (Swerdlow et al., 2017).

In Malta, plasma cell neoplasms accounted for 14% of haematological malignancies between 2000-2007 (De Angelis et al., 2015). Between 2006-2015, there were on average 19 new cases of MM yearly, with an average of 12 deaths yearly. Only two cases were reported in patients younger than 30-years-old (Malta National Cancer Registry, 2017). In Malta, the 1-year and 5-year relative survival for plasma cell neoplasms, were 68.4% and 29.5% respectively; lower than the European average (De Angelis et al., 2015).

Oral manifestation is frequent but rarely the presenting sign. Clinical features include bone pain, fatigue, anaemia, infections and 'punched-out' osteolytic lesions radiographically (Cardoso et al., 2014).

MM is an incurable, progressive disease with frequent relapse. However, outcomes have significantly improved thanks to novel myeloablative treatment and subsequent autologous stem-cell transplant (Cardoso et al., 2014). The survival rate ranges from <6 months to >10 years. Prognosis is poorer in people over 70 years of age, frail individuals and those with co-morbidities (Swerdlow et al., 2017).

CASE PRESENTATION

A 65-year-old male, was referred to the Ear, Nose & Throat (ENT) department by his dentist because of a non-healing lesion measuring 2.2cm in diameter on the right side of the hard palate, medial to the molars. Examination revealed a solitary, exophytic, hard-rubbery mass, having the same colour as the surrounding mucosa, except where ulcerated. It readily bled when manipulated. The patient was otherwise apparently healthy but complained of diffuse joint and back pain.

An initial blood test showed elevated bilirubin, gamma-glutamyl transferase, lactic acid dehydrogenase, C-reactive protein, procalcitonin, magnesium, sodium, chloride and phosphate. Additionally, the patient had hypocalcaemia.

Serum Protein Electrophoresis (SPE) showed elevated levels of Alpha-1 and -2 globulins and reduced Albumin and Gamma Globulin levels. A weak kink of uncertain significance was noted in the gamma fraction but no monoclonal band was detected at this point.

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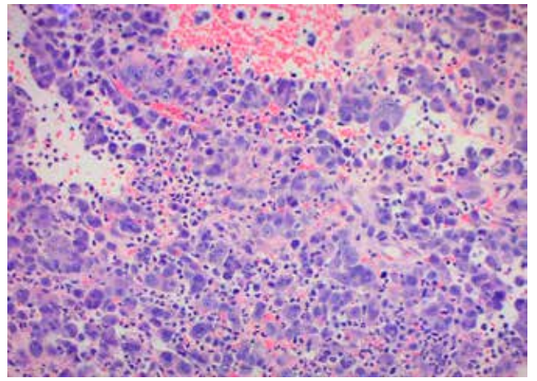

Figure 1. Medium power view showing sheets of tumour cells on a haemorrhagic background. - H&E stain. Original magnification x100

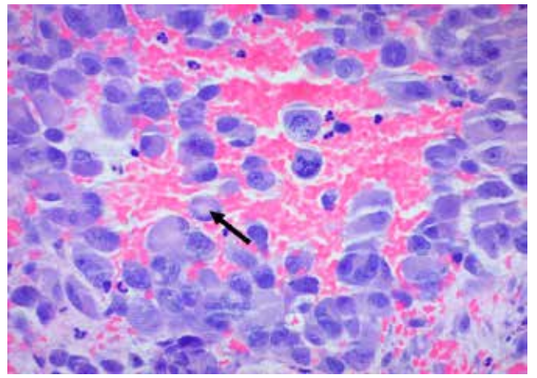

Figure 2. High power view showing tumour cells with eccentric, pleomorphic nuclei, large eosinophilic nucleoli and rather abundant eosinophilic cytoplasm. Some of the tumour cells have a definite plasmacytoid morphology, including a perinuclear hof (arrow). - H&E stain. Original magnification x400.

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Following this, immunofixation was carried out, revealing low IgG levels in the serum and an isolated IgG Lambda monoclonal band.

An incisional biopsy showed mucosa infiltrated by sheets of large malignant cells with pleomorphic, eccentric nuclei, large eosinophilic nucleoli and abundant cytoplasm. Mitotic figures, including atypical forms, were frequent (figs 1, 2).

A large immunohistochemistry panel was carried out (fig 3). The results are summarised in Table 1.

Marker	Result
VS38C	Strong diffuse expression
CD138	Patchy expression
AE1/AE3	Focal expression
Oct2	Focal weak expression
CD45	Weak patchy expression
CD20	Not expressed
PAX 5	Not expressed
CD56	Not expressed
CD 30	Not expressed
HHV8	Not expressed
S100 protein	Not expressed
SOX10	Not expressed
Keratin 5	Not expressed
Keratin 7	Not expressed
Keratin 20	Not expressed
TTF1	Not expressed
CDX2	Not expressed
PAX 8	Not expressed

Table 1. Immunohistochemistry panel carried out on the palate biopsy.

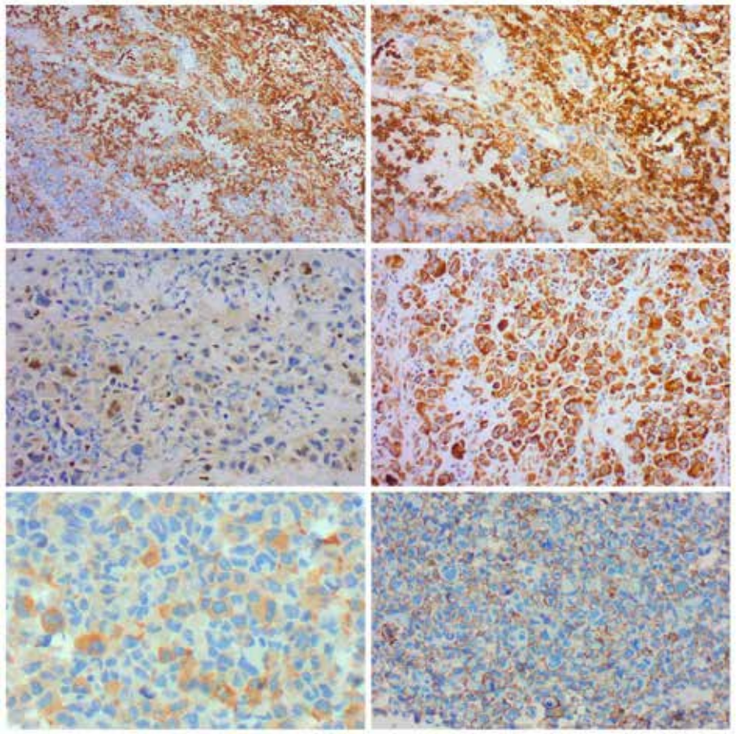

Figure 3. By immunohistochemistry the neoplastic cells expressed (A) CD45: weak patchy expression. (B) CD138: patchy expression. (C) Oct2: focal weak expression. (D) VS38C: Strong diffuse expression (E) Cytokeratin: Weak patchy expression. (F) CD56: Weak diffuse expression.

An initial Pulmonary Computed Tomography Angiography (PCTA) also revealed a mediastinal mass measuring 11mm in diameter.

An Endobronchial Ultrasound (EBUS) guided biopsy of this mass revealed histological and immunohistochemical features almost identical to those described for the palate lesion, except that CD56 was positive in this second biopsy (fig 3F).

These features favoured plasma cell myeloma. Following discussing at the hematopathology multidisciplinary team meeting, it was decided to test for Epstein-Barr Virus (EBV) to exclude plasmablastic lymphoma.

Immunohistochemistry for EBV LMP-1 and EBNA were negative, making plasmablastic lymphoma unlikely. Polymerase Chain Reaction (PCR) for EBV was also performed with negative results.

Following the biopsies, further imaging was carried out. Significant findings are listed in Table 2 on page 10.

In summary, imaging showed both medullary and extramedullary involvement in many parts of the body, indicative of widespread aggressive disease.

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Image	Significant findings
Brain CT scan	• Atrophic parenchymal changes in the brain. • Mildly dilated ventricles. • A lytic lesion in the left parietal bone.
Neck CT scan	• 2.5 cm in diameter lesion posterior to the right side of the maxilla associated with bony involvement (fig 4A, 4B). • 2 cm in diameter mass in the right side of the root of the neck associated with involvement of C7 vertebra. Further lytic lesions in C2, C4, C6 and C7.
Thorax CT scan	• Chronic Obstructive Airways Disease (COAD) changes in the lungs. • Confirmed presence of a pulmonary nodule in the lower right lobe. • Small focal fibrotic changes in the right middle lobe and right base. • Enlarged lymph nodes in the right side of the mediastinum and right hilum (fig 4D) and another in the internal mammary chain. • Several lytic lesions in the thoracic spine. • Several ribs are involved bilaterally (fig 4E).
Abdomen and pelvis CT scan	• 9mm in diameter hypovascular nodule present in the spleen. • Bilateral adrenal nodules likely metastatic. • Simple cysts in both kidneys. • Diverticular changes in sigmoid colon. • Several lytic lesions in the lumbar spine. • Lytic lesions also in the pelvis and both upper femora. • Upper sacrum sclerotic changes were identified. • T1, T4, T8 and L5 demonstrated collapsed vertebral bodies. (fig 4F).
NM WBC Bone scan	• Increased tracer uptake in the right half of the maxilla (fig 4C). • A focus noted in the frontal bone, the 7th left rib, L5 and the sternal body. • An area with abnormal density was also noted in T8.
MRI Whole Spine	• Extensive marrow infiltrative disease seen at multiple levels in the cervical and thoracic spine without cord compression. • Soft tissue mass seen extending out of C6 vertebral body on the right side, into prevertebral space. • Multiple thoracic vertebrae manifest infiltrative disease which extends into the extradural space.
PCTA (Repeated)	• The 13mm nodule in the right lower lung lobe remained unchanged. • Emphysematous changes. • New ground glass change in the upper left lobe and in the middle lobe. • Multiple lytic rib and vertebral lesions. Multiple pathological fractures and loss of height of the T8 and T4 vertebrae were noted.
NM PET/CT Scan	• Avid nodal, right lung, adrenal, pancreatic, soft tissue, spleen and multiple skeletal lesions.
Brain CT scan (Repeated)	• Diffuse cerebral and cerebellar atrophic changes and multiple lytic lesions within the skull.

Table 2. Imaging techniques used and the significant findings of each.

Diagnosis was based on the demonstration of an isolated monoclonal band clinically, the immunohistochemical and microscopic features and the multiple, disseminated lytic lesions observed radiographically.

A specific chemotherapy protocol is utilised for multiple myeloma and plasma cell leukaemias in Malta; bortezomib, lenalidomide & dexamethasone (VRd). However, due to the widely disseminated disease status in this case, a more radical approach was utilised comprising; bortezomib, dexamethasone, lenalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide (VDTPACE).

The goal of treatment was to get the patient into remission, after which an autologous bone marrow transplant was planned. Our patient showed no response to treatment and due to debilitating side effects of the chemotherapy, it was decided to shift to palliative care. The patient unfortunately passed away within two months of diagnosis.

Unfortunately, no photographs of the lesion in the palate were taken as this patient was in a rapidly declining condition and we did not wish to inconvenience him further.

DISCUSSION

MM is thought to arise in the setting of chronic antigenic stimulation through infection, chronic diseases, exposure to certain toxic substances or radiation, however such exposure is not always identified.

Antigenic stimulation is believed to produce multiple plasma cell clones, one of which may undergo malignant transformation following a mutagenic event (Orazi et al., 2014). Most MMs arise in patients who had a precursor monoclonal gammopathy of undetermined significance (MGUS) (Swerdlow et al., 2017). Genetic polymorphism may contribute to the aetiology; however, the correlation is weak (Orazi et al., 2014).

The most common symptoms are due to hyperCalcaemia, Renal insufficiency, Anaemia and Bone lesions (CRAB) causing nausea, weight-loss, shortness of breath and bone pain amongst others. Additional findings include infections, bleeding and neurological manifestations secondary to spinal cord compression or peripheral neuropathy.

Considering the wide dissemination of disease, the symptoms in our patient were unexpectedly subclinical. He presented with a non-resolving swelling as the first sign of disease, which was secondarily ulcerated possibly following trauma (Romano et al, 2014). The only complaints besides the swelling in the palate were non-specific back-pain and diffuse joint pain. Oral manifestations of MM often occur (~35%), but rarely as the first manifestation (Romano et al., 2014). The main clinical features found intraorally are shown in Table 3 (de Almeida et al., 2018).

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Oral clinical manifestation	Percentage
Swelling	65.4%
Bone pain	33.3%
Paraesthesia	27.1%
Amyloidosis lesions	11.1%
Bleeding gums	9.8%
Tooth mobility	6.1%
Root resorption	3.7%
Gingival swelling	1.2%
Candidiasis	1.2%

Table 3. Oral manifestations reported in 81 patients with MM (Modified from de Almeida et al., 2018).

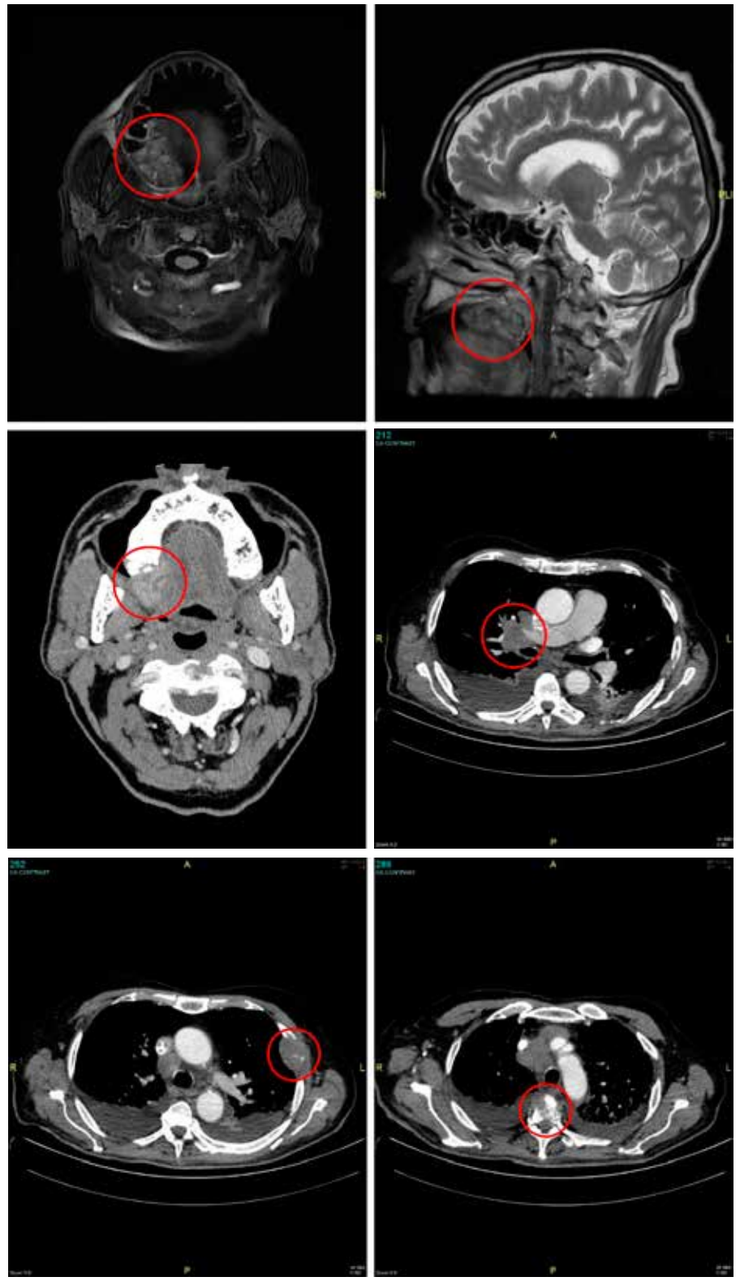

Figure 4. Imaging showing medullary and extramedullary involvement. Pathologies described are circled in red. (A) Axial view of MRI showing a bony lesion in the upper right palatine bone and posterior maxilla. (B) Sagittal view of MRI showing bony lesion in the upper right palatine bone and posterior maxilla. (C) Image from a bone scan showing increased tracer uptake on the right maxilla, posterior to the molars. (D) Axial CT slice showing enlarged hilar lymph nodes on the right side. (E) Axial CT scan showing rib involvement on the left side. (F) Axial CT scan showing collapse of a collapsed thoracic vertebra.

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Laboratory investigations in most cases reveal hyperuricemia (in 50%), high creatinine (~25%), hypercalcaemia (20%) and hypoalbuminemia (~15%) (Orazi et al., 2014). M proteins (abnormal immunoglobulin components) are found in the urine or serum in around 97% of cases, the frequency of which are shown in Table 4.

The remaining 3% are non-secretory. Immunoglobulin light chains demonstrated in urine are termed Bence Jones proteins. Renal damage occurs following renal tubular reabsorption of this protein (Swerdlow et al., 2017).

In our case, hypoalbuminemia and M protein (light chain) were present with no evidence of renal insufficiency, anaemia or Bence Jones protein. Since bone destruction occurs in MM, one would expect a patient to be hypercalcaemic (Swerdlow et al., 2017). Unexpectedly our patient had persistent hypocalcaemia of unknown cause prior to treatment.

There are multiple possible mechanisms for the development of hypocalcaemia; drugs (chemotherapeutic agents & bisphosphonates), osteoblastic bone metastases, hypoparathyroidism, infections, renal failure, and malnutrition. Tumour lysis syndrome has also been described, particularly in haematological malignancies with rapid cellular turnover. The breakdown of cells releases phosphates into the bloodstream. Calcium is precipitated to form calcium phosphate, leading to hypocalcaemia (Gonçalves et al., 2019).

Histologically, the plasma cells in MM vary from mature forms indistinguishable from normal cells, to immature blasts and pleomorphic cells (Swerdlow et al., 2017). In this case, the histological picture was of a high-grade malignancy.

Diagnosis was difficult because the morphology was not typical of plasma cell neoplasms, hence the large immunohistochemical panel. Immunohistochemistry is useful in identifying plasma cells, confirming monoclonal proliferation and in distinguishing MM from other neoplasms (Swerdlow et al., 2017). The observance of sheets or inter-fatty spaces filled with plasma cells on a CD138- or MUM1-stained slide, is diagnostic of MM (Orazi et al., 2014). Markers usually tested for are shown in Table 5.

Marker	Significance
CD138	Useful for quantifying plasma cells and clonality. (Non-specific)
MUM1	Useful for identification of plasma cell differentiation. (Non-specific)
CD56 & KIT (CD117)	Used to detect populations of neoplastic plasma cells. (Often expressed in MM)
CD20	Expressed by small-cell or lymphoplasmacytic variant of MM.
MYC	Increased expression may be detected in MM.

Table 5. Markers used in immunohistochemistry to aid diagnosis of MM.

Plasma cells are terminally differentiated B lymphocytes. During maturation plasma cells lose expression of CD45 and of CD20 and gain expression of CD138. Immunohistochemistry in our case demonstrated weak, patchy expression of CD45 (fig 3A) and stronger patchy expression of CD138 with negative CD20.

This suggests abnormal plasma cells with heterogenous maturity. The focal, weak expression of Oct2 seen (fig 3C) indicates limited retention of B cell markers by plasma cells. VS38C, a very sensitive but not specific plasma cell marker showed strong, diffuse expression (fig 3D), further suggesting neoplastic plasma cells. CD56 (fig 3F), is not normally expressed by plasma cells, but aberrant expression in MM is typical and expression of this antigen in our case confirmed the neoplastic nature of the infiltrate.

Cytokeratin expression was weak and patchy (fig 3E). This was interpreted as aberrant cytokeratin expression by malignant plasma cells. Overall, the immunoprofile favoured MM over carcinoma. CD117 and MYC were not tested for and MUM1 was negative.

On radiographical skeletal survey, bone lesions are identified in about 70% of cases of MM, frequently by MRI and PET/CT. Bone lesions encountered are shown in Table 6.

M protein	Frequency
IgG	50%
IgA	20%
Light chain	20%
IgD, IgE, IgM or Biclonal	10%

Table 4. Frequency of M proteins found in the urine or serum (Modified from Swerdlow et al., 2017).

Bone Lesions	Frequency
Lytic lesions	~70%
Osteoporosis	10—15%
Pathological fractures	15—20%
Vertebral compression fractures	

Table 6. Frequency of different bone lesions found in MM

The most frequent sites are the vertebrae > ribs > skull > shoulders > pelvis > long bones (Swerdlow et al., 2017). Our patient had generalised and multifocal bone marrow involvement, evidenced by lytic lesions demonstrated radiographically in bones all over the body. The back-pain the patient experienced could have been caused by the lytic bone lesions causing vertebral compression (Dingli & Cook., 2004), while joint-pain in some patients could be caused by direct myelomatous joint infiltration (Molloy et al, 2007), however, this was not definitely identified in this case.

Our patient also had a bone lesion in the maxilla. De Almeida and colleagues report that 90.1% of patients with oral manifestations of MM exhibited bone lesions in the jaws, a number of which were identified using imaging techniques used routinely in dentistry, including skull, periapical and panoramic views. 80.2% were plasmacytomas (well-defined, marked erosion, expansion and destruction of the bone cortex) and the remaining 9.8% had "punched out" lesions.

Bone lesions mostly occurred in the mandible. The majority presented with an associated intraoral swelling (de Almeida et al., 2018). Our patient also had extensive soft tissue disease seen radiographically at presentation. This led to an initial clinical working diagnosis of disseminated carcinoma, possibly from a lung primary. Extramedullary involvement is a feature of advanced disease (Swerdlow et al., 2017). It has been reported in 7—18% of newly diagnosed MM cases. Extramedullary disease may develop later in the course of the disease in about 6 – 20% of cases (Bladé et al., 2012).

Other diseases formed part of the differential diagnosis other than a poorly differentiated carcinoma. Plasmablastic lymphoma often presents in the oral cavity in immunocompromised individuals. The neoplastic cells in this lymphoma resemble immature plasma cells and have a CD20-negative plasmacytic phenotype. Practically all cases show an association with EBV infection.

This diagnosis was excluded in this case as the patient was not immunocompromised and EBV was not identified by PCR. Additionally, HHV8-assocaited lymphoproliferative disorders were considered, which present with generalised lymphadenopathy and immature plasmacytoid lymphoproliferations. Most cases are co-infected with EBV. These disorders were ruled out as EBV and HHV8 were negative (Swerdlow et al., 2017).

Diagnostic criteria (Appendix B) for MM are outlined by the International Myeloma Working Group (IMWG) (Rajkumar et al., 2014). Diagnosis of MM was consequently based on histology, demonstration of an isolated IgG Lambda monoclonal band and through the multiple and widely dispersed lesions seen radiographically.

Systemic treatment is usually used for most cases of MM. Drug therapy usually consisting of 2 or 3 different drugs used in combination to elicit better response. Initial therapy depends on drug availability in different countries.

Regimens commonly used in the initial treatment of MM include:

i. Lenalidomide plus dexamethasone (Rd);
ii. Bortezomib, lenalidomide, dexamethasone (VRD);
iii. Bortezomib, thalidomide, dexamethasone (VTD);
iv. Bortezomib, cyclophosphamide, dexamethasone (VCD).

In patients who are eligible for bone marrow transplant, initial therapy with VRD or VTD regiments are preferred (Rajkumar and Kumar., 2016). Treatment in Malta follows the VRD protocol used for the treatment of MM and plasma cell leukaemia by the National Health service (NHS), laid out by the Network site specific group (NSSG).

High-dose chemotherapy is administered to kill the bone marrow cells and then an autologous bone marrow transplant is performed. Due to the aggressive nature of the disease in our case, VDTPACE/ DTPACE protocol (Appendix A) was used (NSSG., 2018). In Malta, Thalidomide is substituted for Lenalidomide as per local protocol.

Patients with symptomatic myeloma are often given bisphosphonates to reduce bone pain and fracture, our patient was not given these (Cardoso et al., 2014). Surgery and radiation therapy are sometimes used where the disease is localised and/or in areas that do not respond to chemotherapy (American Cancer Society., 2018). In our case, although there was no response to chemotherapy, the disease was too widespread to carry out surgery or radiotherapy on all affected sites.

CONCLUSION AND LEARNING POINTS

Multiple Myeloma is the most common and important plasma cell neoplasm. Signs and symptoms usually occur as a result of organ infiltration by aberrant plasma cells and by abnormal chemical properties of immunoglobulins produced.

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The physical manifestations of this disease are infrequent; therefore, diagnosis of MM generally occurs after the onset of symptoms of organ damage, possibly when it is too late. Without treatment MM is a terminal illness. Oral manifestations are present in around 35% of patients.

The most common clinical and radiologic signs are swellings and osteolytic lesions respectively. Oral manifestations are rarely the presenting feature. It is imperative that dentists are familiar with the clinical and radiographic manifestations suggestive of this disease, as early disease recognition may lead to increased survival and prognosis.

Failure to do so could lead to misdiagnosis or late diagnosis of MM. Furthermore, dentists play a role in prevention of oral complications, particularly bisphosphonate-related osteonecrosis of the jaw in patients who commence antiresorptive therapy. In addition, treatment with immunosuppressive drugs is associated with higher caries and periodontal disease rates (de Almeida et al., 2018) which need to be managed by the dentist.

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APPENDIX A: DRUGS USED AS PART OF THE VDTPACE REGIME

Myeloma group

NHS
Thames Valley
Strategic Clinical Network

DRUG REGIMEN

Days	Drug	Dose	Route	Comments
1 to 4	**Dexamethasone**	40 mg daily	Oral	
Continuous daily/ If PBSC harvest planned only for days 1 to 4	**Thalidomide (See note below)**	Start 50 mg and increase up to 100 mg as tolerated	Oral	Nocte
1 to 4	**Cisplatin** *	10 mg/m²/day [total dose per cycle 40 mg/m²]	Continuous intravenous infusion through Hickman line	Daily dose of Cisplatin and Etoposide combined in a 1 litre 0.9% sodium chloride bag and infused over 24 hours
	Hydration	1L 0.9% sodium chloride with 20 mmol KCl (potassium chloride) and 8 mmol magnesium sulphate 12 hourly	Continuous intravenous infusion	
1 to 4	**Etoposide** *	40 mg/m²/day [total dose per cycle 160 mg/m²]	Continuous intravenous infusion through midline	Daily dose of Cisplatin and Etoposide combined in a 1 litre 0.9% sodium chloride bag and infused over 24 hours
1 to 4	**Cyclophosphamide***	400 mg/m²/day [total dose per cycle 1600 mg/m²]	Intravenous Bolus injection	Daily dose of cyclophosphamide administered as a bolus injection
1 to 4	**Doxorubicin** *	10 mg/m²/day [total dose per cycle 40 mg/m²]	Continuous intravenous infusion **must be through a central Hickman line**	Daily dose of doxorubicin in 100 ml of sodium chloride 0.9% and infused over 24 hours
Day 5	**GCSF**	Filgrastim 0.5 miu/kg daily from day 5 until neutrophils > 1.0 x 10^9/L. Filgrastim 1 miu/kg from days 5 onwards if harvesting PBSCs, with aim to collect on days 15 – 16.		
1, 4, 8 and 11	**Bortezomib**	1.0 mg/m²	S/C bolus	***Only where Bortezomib is indicated***

* It is reasonable to consider capping at BSA of 2 m² in selected patients

APPENDIX B: IMWG CRITERIA FOR MM DIAGNOSIS

Clonal bone marrow plasma cells >10%
or Biopsy-proven bony or extramedullary plasmacytoma

+ ≥ 1 of the CRAB features	**Hypercalcemia:** serum calcium > 0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11mg/dL)
	Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177mol/L (>2mg/dL)
	Anaemia: haemoglobin value of >20g/L below the lowest limit of normal, or a haemoglobin value <100g/L
	Bone lesions: ≥ 1 osteolytic lesion on skeletal radiography, CT, or PET/CT. If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement
Or None of the above ≥ 1 of the myeloma-defining events	≥ 60% clonal plasma cells on bone marrow examination
	Serum involved / uninvolved free light chain ratio of ≥ 100, provided the absolute but level of the involved light chain is at least 100mg/L
	More than one focal lesion on MRI that is at ≥ 5mm

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FABRICATION OF AESTHETIC MOCK-UPS USING A DIGITAL WORKFLOW AND ITS CLINICAL RELEVANCE

By Dr Sarah Pace Moore BChd MSc Restorative Dentistry (Edin)

As dental professionals our goal is to provide our patients with an aesthetic, functional and predictable outcome.

Improving a patients' smile requires adequate planning, which is key to success. The use of diagnostic mock ups, which can be fit and assessed on the patient's dentition, facilitates and improves prothesis design.

A mock-up can be fabricated using analogue or digital techniques. Understanding the pros and cons of both techniques is important so as to select the most appropriate technique for different clinical situations.

Besides providing the patient with a "smile preview", mock-ups enable a dentist to evaluate the aesthetics and to complete a diagnostic assessment.

At this stage issues could be anticipated and any adjustments for an improved aesthetic outcome can be performed. It gives the opportunity to explain and inform the patient about additional treatment such as orthodontic, periodontal or surgical treatments necessary prior initiating the restorative work.

The best treatment options in terms of techniques and materials is further discussed with the patient to be able to make an informed decision. Digital smile designs have shown to improve patient-dentist communication, increased patient acceptance and higher patient satisfaction with the final restorative work.[1]

Traditionally, the dentist would take a silicone impression together with a bite registration, to prepare an articulated study model. The dental technician prepares a wax up and provides the dentist with a silicone key index.

The dentist would then fabricate a mock-up over the patient's teeth using the self-curing provisional material such as bis-acryl.[2]

During our visit to the Zirkonzahn military school, we were instructed on the digital workflow to create a milled mock-up. This approach facilitates aesthetic treatment planning and enhances patient communication. As more dentists are shifting towards using digital systems it is important to understand how and what are the procedures to create digital mock-up splints.

Initially, an intra oral scan is taken and uploaded on the software to create a digital model. Three photographs or face scans are needed, one with closed lips, another with slightly open lips and a final smile with exposure at least up to the lateral incisors.

Face scans/ photographs are cut and positioned in the background and superimposed on the digital model using the Zirkonzahn software (The Modifier) so as to reproduce the patients' smile. Teeth from the digital library are adapted onto the digital model.

At this stage the technician can adjust the teeth individually, modifying the tooth morphology accordingly. The smile design can be shown to the patient and adjusted according to patient preference prior to fabrication.

Whilst designing the mock up a steep path of insertion should be selected. This ensures that an exact marginal seal can be generated in the cervical area.

The Shimbashi Technique, first described by Hank Shimbashi, is used to achieve the best aesthetic outcome and tooth proportion. It determines the vertical component of occlusion during closure.

This technique aims to establish the ideal tooth length from the width of the upper incisors. In addition, it provides an ideal occlusal vertical dimension by proposing the ideal distance between the maxillary central incisors gingiva-enamel junction to the mandibular central incisor gingiva-enamel junction.[3]

Once dentist, technician and patient are satisfied with the digital design, it is ready for processing.

The digital model is positioned on the digital block, further tags

Ideal width mm	Ideal Length mm	Ideal Shimbashi-dimension mm
7	9	14.5
7.5	9.75	15.75
8	10.5	17
8.5	11	17.75
9	11.5	18.5
9.5	12.25	20
10	13	21
10.5	13.5	22

are inserted by the technician and modified, once set it is milled and polished, prior to the trial phase.

The Mock up stage allows careful assessment of the:

- Shape and size proportion
- Tooth morphology
- Tooth position (alignment and inclination of teeth)
- Buccal corridor space
- Assessment of incisal edge along the smile line
- Lip position
- Phonetics

The material used is the Zirkonzahn Temp Premium Flexible. This new material is a highly flexible resin with improved properties, very strong, durable and comfortable. It allows the patient to have a trial period with their new dental setup, allowing them to evaluate them functionally, aesthetically and phonetically.

In addition, it gives the patient the opportunity to show it to their friends and relatives and provides adequate time for the patient to make an informed decision. Throughout the trial phase any changes required can be relayed back to the technician and adjusted on the digital model for the final restorations.

With the Zirkonzahn flexible Mock-up, no bonding is required as it attains retention by engaging the undercuts.

Producing a mock up using a digital workflow could result to be more reliable when compared to traditional methods, which will ultimately affect patient acceptance of the proposed treatment plan.[4]

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ZIRCONIA BONDING

By Brendan Cini B.Ch.D, MFDS RCSEd

The application of zirconia in restorative dentistry has been recognized for a while, mostly because of its excellent biocompatibility, high fracture toughness, radiopacity and color density. Zirconia as a material has evolved greatly from its more traditional application primarily as a structural and posterior restorative material, with modern zirconia materials exhibiting exceptionally good aesthetics as seen in the Zirkonzahn Prettau® family of materials. However, zirconia's inertness poses a particular and consistent issue of poor adhesion and thus poor bond strength (Reddy et al., 2012, Bona et al., 2015). This is a noteworthy challenge in the application of zirconia restorations into the ever-growing field of minimal and no prep restorative treatment where macro-mechanical retention factors are not applicable.

It therefore comes as no surprise that the use of an adhesive cement system is indicated in cementation of dental ceramics restorations (Reddy et al., 2012). These adhesive systems rely on the physico-chemical interaction of the ceramic and cement. While chemical bonding mechanisms using an adhesive/cement system containing ceramic primers, such as phosphate-based monomers (e.g., MDP) are available for bonding zirconia, these need to be coupled with other methods of surface preparations in order to provide an adequate bond, fit for intra-oral service and with its unique challenges (Bona et al., 2015; Tzanakakis et al., 2016).

Zirconia is termed as an acid-resistant ceramic, and so the use of acid/s for bond surface preparation (as used with other ceramic materials such as lithium disilicate ceramics) is not indicated (Calvert, 2010; Reddy et al., 2012; Scaminaci Russo et al., 2019). The literature describes two main methods to improve micromechanical bonding in zirconia: airborne particle abrasion (APA) systems (often termed as sandblasting), and the use of coarse diamond rotary instruments (Scaminaci Russo et al., 2019). The literature unequivocally reports that airborne particle abrasion using alumina particles produces the greatest surface roughness (Tzanakakis et al., 2016; Thammajaruk et al., 2017; Scaminaci Russo et al., 2019). This alteration of the surface topography results in increase of the surface area and improves the wettability of the zirconia by the adhesive, which in turn improves the bonding ability and thus the bond strength (Tzanakakis et al., 2016; Thammajaruk et al., 2017; Scaminaci Russo et al., 2019).

A modification of this is the use of silica-coated alumina particles for air abrasion which results in silicatization (silica coating) of the surface. This silica layer is created through the high-speed impact of the silica-coated alumina particles on the ceramic surface, penetrating the surface (Bona et al., 2015; Khan et al., 2017). This in turn can be used along with a silane coupling agent to enhance the bond with an adhesive resin through chemical bonding. The accepted and evidence-based clinical strategies to resin bond acid-resistant ceramic restorations as in zirconia are:

1. The use of APA using alumina particles to improve the mechanical retention used along with a chemical bonding mechanism through the use of an adhesive/cement system containing ceramic primers, such as phosphate-based monomers, e.g., MDP.

2. The use of APA using silica-coated alumina particles to improve the mechanical bonding while introducing an irregular silica layer onto the ceramic surface to allow the use of a silane coupling agent, which promotes a chemical bond to any resin-based adhesive/cement system.

While other bonding techniques are showing promising in vitro results (Khan et al., 2017), the methods described above have been shown to have positive results both in vitro and in vivo studies with bond strengths and survival rates (75%-100%) comparable to other widely accepted and successful restorative materials (Bona et al., 2015). This coupled with the excellent advancement and development of highly aesthetic and hard-wearing zirconia-based materials supports and maybe even favors the use of zirconia in minimal preparation restorations, particularly given the importance of tooth tissue preservation.

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ORAL LEUKOPLAKIA OF THE FLOOR OF THE MOUTH

SHOULD IT BE TREATED DIFFERENTLY?

Author: Dr Hannah Debono MDS (Melit)
Tutor: Dr Gainza DDS PhD

ABSTRACT

Oral leukoplakia is the most common potentially malignant condition encountered in the oral cavity. Throughout the past decades the definition, means of diagnosis, prediction of malignant transformation and management have been a frequent topic of discussion. In this report, a case of oral leukoplakia on the floor of the mouth of a 43-year-old patient is described, together with the process of diagnosis and subsequent management.

The significance of oral leukoplakia lies in its increased risk of undergoing malignant transformation into oral squamous cell carcinoma. Oral cancer is occurring at an ever increasing prevalence and has a poor 5-year survival rate of less than 50%, primarily due to late presentation. Therefore the diagnosis and appropriate management of oral leukoplakia are critical.

The current predictive factors used in assessing the risk of malignant transformation are discussed, and include the presence and severity of dysplasia, site, size, clinical presentation, duration of lesion, patient factors and molecular markers.

Currently, the gold standard for diagnosis and prediction of risk of malignant transformation is the presence and severity of dysplasia. However, lesions without dysplasia may still undergo malignant transformation and therefore considering dysplasia alone is not always reliable.

Although several studies have already been carried out, there is yet to be a reliable molecular marker determined for the prediction of the malignant transformation of oral leukoplakia.

This highlights the need for further research in order to understand the critical molecular events driving malignant transformation, whereby oral leukoplakia could be managed appropriately and subsequently reduce the associated cancer-specific morbidity and mortality.

KEYWORDS

Oral leukoplakia, potentially malignant lesions, malignant transformation, predictive factors

INTRODUCTION

Oral leukoplakia is a clinical term used to describe a potentially malignant lesion which can be defined as: “a predominantly white, non-wipeable lesion of the oral mucosa having excluded other well-defined predominantly white lesions clinically, histopathologically or by the use of other diagnostic aids”. (van der Waal, 2019)

In the past the definition of leukoplakia has undergone several modifications, the above is a simplified definition suggested in a recent report in 2019 by van der Waal.

Oral potentially malignant disorders are recognisable localised or widespread mucosal diseases which may display either epithelial dysplasia or less commonly oral squamous cell carcinoma at their initial presentation.

Lesions which are not malignant, harbour a considerably higher but also unpredictable risk of undergoing malignant transformation and developing squamous cell carcinoma. Malignancy may develop at or adjacent to the site of the leukoplakia, or at any other site within the oral cavity and head-and-neck area. (Nadeau & Kerr, 2018; Villa & Woo, 2017)

Oral leukoplakia is the most common oral potentially malignant lesion, affecting 0.1% to 4.9% of the world population and has a reported annual risk of malignant transformation ranging from 2% to 36%, varying according to geographic location. (van der Waal, 2019; Gopinath et al., 2016)

This paper describes a case of oral leukoplakia on the floor of the mouth. It aims to discuss the several somewhat predictive factors of malignant transformation that have currently been established, as well as those which are continuously being studied in order to obtain reliable means of predicting the malignant transformation of oral leukoplakia.

This is critical as it will aid in the appropriate management of such lesions, and subsequently reduce the cancer-specific morbidity and mortality. (van der Waal, 2019; Goodson et al., 2015; Nadeau & Kerr, 2018)

CASE PRESENTATION

A 43-year-old male patient presented to the University Teaching Clinic on referral by a GDP for review of a white plaque on the floor of the mouth of unknown time of evolution. Medical and family histories were non-contributory. The patient had a tobacco smoking history of 17 years and at the time of examination, smoked 20 cigarettes per day (17 pack years). He admitted to drinking alcohol on weekends but did not specify amounts consumed.

On extraoral examination, no facial asymmetries were observed. No palpable lymph nodes were detected. On intraoral examination, a unilateral white homogenous plaque on the right side of the floor of the mouth was observed. The plaque extended anteroposteriorly from the lingual aspect of the lower right central incisor to the lower right first molar, and up to the lingual frenum.
The lesion measured 1.5 x 0.7 cm (Figure 1).

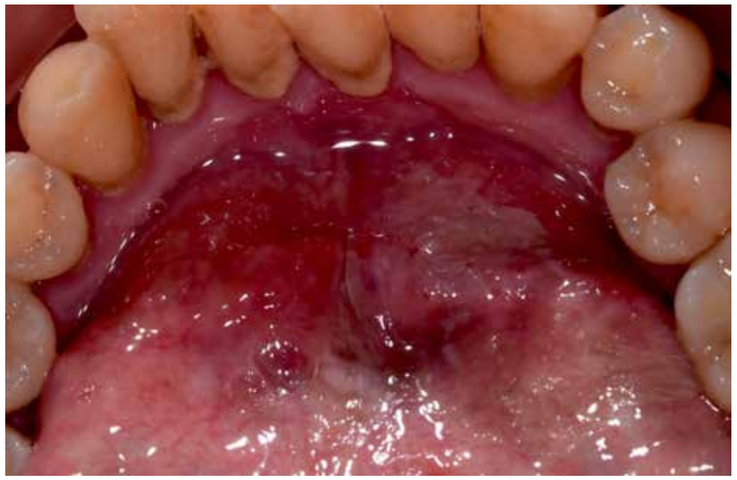

Figure 1: White homogenous plaque on the right floor of the mouth

Figure 2: Biopsy specimen from the floor of the mouth

The plaque was non-tender to palpation and of similar consistency to the surrounding peri-lesional mucosa. It did not rub off with gauze. No contact bleeding was observed on palpation. There were no signs or possible causes of trauma in the area.

Apart from the white plaque on the floor of the mouth, two other white homogenous plaques were observed, one on the right retromolar pad and the other on the left retromolar pad. The plaque on the right measured 0.7 cm in diameter, whilst the one on the left measured 0.5 cm in diameter. These plaques had similar characteristics to the plaque observed on the floor of the mouth.

The patient had poor oral hygiene. BPE scores of 3 were found in three out of the six sextants. Multiple carious lesions were also present.

Based on oral findings and smoking history, a clinical differential diagnosis of the white plaques was made, including:

1. leukoplakia
2. frictional keratosis
3. lichen planus
4. oral squamous cell carcinoma

An incisional biopsy of the white plaque on the floor of the mouth was performed on the same day of presentation, and the specimen obtained was sent for histological examination. (Figure 2)

Initial management of the patient involved oral hygiene instructions and smoking cessation advice, including education about the tobacco quit hotline and nicotine replacement therapy.

The histopathological analysis showed a stratified squamous epithelium with hyperkeratosis and focal parakeratosis. There was a focal lichenoid-like lymphocytic inflammatory infiltrate. The biopsy showed no signs of dysplasia or malignancy. (Figures 3 and 4)

The treatment plan involved reviewing the lesions every four weeks and continued smoking cessation advice.
In theres reviews, no changes in the size of the lesions was observed and the texture, colour and other characteristics remained consistent. There was also no change in the patient’s smoking habits.

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ORAL LEUKOPLAKIA OF THE FLOOR OF THE MOUTH

SHOULD IT BE TREATED DIFFERENTLY?

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After several appointments, the patient's compliance with attendance was poor, and multiple appointments were missed.

DISCUSSION

Oral cancer is one of the most common types of cancer worldwide, and accounts for more than 300,000 new cases annually. In Malta, there are approximately 31 new cases every year.

The majority of oral squamous cell carcinoma cases are preceded by potentially malignant conditions. Considering the significant morbidity and mortality as well as a poor 5-year survival rate of less than 50%, both primary and secondary prevention of oral cancer are critical. (Nikitakis et al., 2018; WHO, 2019)

Secondary prevention of oral cancer could be achieved by identifying the potentially malignant lesions at high risk of undergoing malignant transformation and subsequent appropriate treatment. Current research is focused on identifying predictive factors of malignant transformation. The factors currently being developed and utilised include: dysplastic changes observed in the histopathological analysis, molecular and genetic characteristics and clinical characteristics of the patient and the lesion. These are discussed below.

To date, the histopathological grading of epithelial dysplasia remains one of the most important features in characterisation of mucosal lesions, as well as the most reliable predictor of malignant potential. (Gopinath et al., 2016; Nikitakis et al., 2018) Dysplasia is characterised by architectural disturbance accompanied by cytologic atypia. (Table 1)

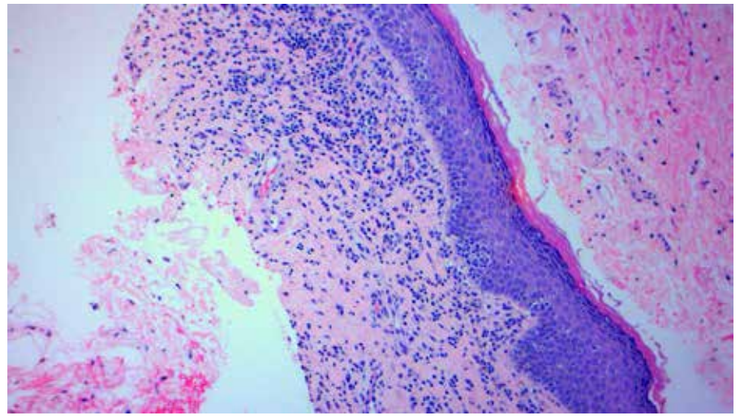
Figure 3: Low power view (H&E, 4x) of the biopsy sample showing a chronic inflammatory infiltrate in the lamina propria.

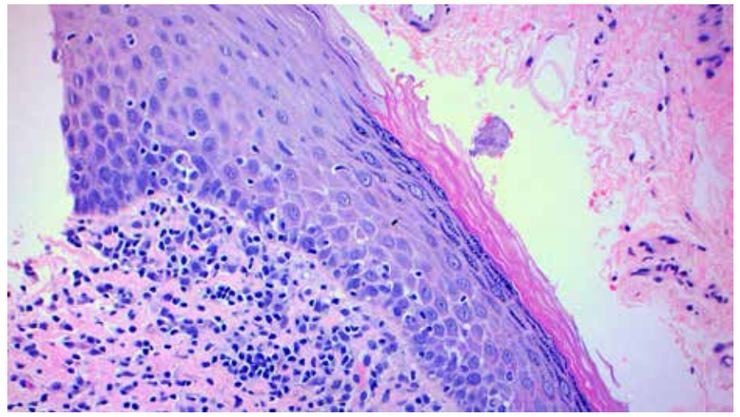
Figure 4: Medium power view (H&E, 10x) showing a well structured epithelium with hyperkeratosis, lymphocyte migration extending into the basal layers of the surface epithelium with associated basal cell vacuolar damage and occasional Civatte body formation.

The severity depends on the proportion of epithelium involved in these changes: the basal third; mild dysplasia, extension into the middle third; moderate dysplasia, extension into the upper third; severe dysplasia and extension into the full thickness of the epithelium; carcinoma in situ. (Nadeau & Kerr, 2018)

Dysplasia can be used to classify oral leukoplakia according to its risk of malignant transformation: low risk; mild and moderate dysplasia, and high risk; severe dysplasia and carcinoma-in situ. (Ho et al., 2012)

It has shown to be a good predictor of malignant transformation for higher grades of dysplasia, but it is a relatively poor predictor for low grade dysplasia, which represent the majority of lesions. (Rock et al., 2018)

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However, presence of dysplasia does not guarantee future malignant transformation, nor does the absence of dysplasia preclude the potentially malignant nature of the oral leukoplakia and assessment of dysplasia carries a degree of subjectivity. (van der Waal, 2019; Nikitakis et al., 2018)

The site of oral leukoplakia may also predict the risk of malignant transformation. Oral leukoplakia on the floor of the mouth and ventrolateral tongue have consistently shown a higher malignant potential among several studies.

Some studies also include the soft palate complex (including the retromolar area). These sites were labelled high risk sites, whilst the remaining sites of the oral cavity were designated as low risk. (Nadeau & Kerr, 2018; Zhang et al., 2001)

This classification is supported by the findings that: lesions from high risk sites more frequently demonstrate dysplasia and loss of heterozygosity, a significantly higher percentage of potentially malignant lesions at high risk sites undergo malignant transformation into carcinoma, and the majority of oral squamous cell carcinoma is seen at high risk sites. (Zhang et al., 2001)

The size of oral leukoplakia has also shown to affect the risk of malignant transformation. In fact, lesions larger than 200mm2, have shown more than a five-fold increase in the risk of malignant transformation. (Nadeau & Kerr, 2018; Ho et al., 2012)

Oral leukoplakia can also be classified according to its clinical presentation, and two subtypes exist; homogenous and non-homogenous, shown in Table 2. (Nadeau & Kerr, 2018)

ARCHITECTURE	CYTOLOGY
irregular epithelial stratification	anisonucleosis
loss of polarity of basal cells	nuclear pleomorphism
drop-shaped rete ridges	anisocytosis
increased number of mitotic figures	cellular pleomorphism
premature keratinisation in single cells	increased nuclear to cytoplasmic ratio
keratin pearls in rete ridges	increased nuclear size
suprabasal mitotic activity	atypical mitotic figures
cell crowding	increased number and size of nucleoli
	nuclear hyperchromasia

Table 1: Architectural and cytological features of dysplasia (Rezezi et al., 2017)

HOMOGENOUS	NON-HOMOGENOUS
flat, thin, uniform white plaques	non-uniform
	i) erythroleukplakia mixed red and white lesion, not predominantly white
	ii) speckled leukoplakia a mixed red and white lesion, predominantly white
	iii) nodular or verrucous leukoplakia

Table 2: Clinical presentations of oral leukoplakia (Nadeau & Kerr, 2018)

Non-homogenous lesions have a significantly higher chance of exhibiting epithelial dysplasia on histological examination, and have shown a higher rate of malignant transformation when compared to homogenous leukoplakia.

Furthermore, non-homogenous oral leukoplakia showed a significantly higher risk of containing foci of carcinoma at the time of diagnosis, with the verrucous subtype showing the greatest risk, followed by the speckled subtype. (Gopinath et al., 2016; Ho et al., 2012)

The duration of oral leukoplakia is another factor which has been linked to malignant transformation. Studies have shown that the longer the duration, the higher the incidence of oral cancer, with an increased risk for malignant change in the first 5 years. (Villa & Woo, 2017; Napier & Speight, 2008)

Several patient factors have also been shown to affect the risk of malignant transformation, including gender, age and smoking habits.

The female gender as well as patients aged between 45 to 65, have shown an increased risk of oral leukoplakia undergoing malignant transformation. (Nadeau & Kerr, 2018; Villa & Woo, 2017; Deliverska, 2017)

Smokers are more likely to develop oral leukoplakia and oral epithelial dysplasia than non-smokers, in fact studies have shown a six fold increase in risk among smokers.

However, when oral epithelial dysplasia does occur in non-smokers,

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ORAL LEUKOPLAKIA OF THE FLOOR OF THE MOUTH

SHOULD IT BE TREATED DIFFERENTLY?

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they are more likely to undergo malignant transformation compared to smokers. (Nadeau & Kerr, 2018; Ho et al., 2012; Rock et al., 2018)

Therefore clinicians should be diligent in oral mucosal screening in all patients, regardless of their tobacco habits since, although tobacco is one of the strongest risk factors for oral squamous cell carcinoma, for patients with histologically confirmed oral epithelial dysplasia, the non-smoking cohort is at an increased risk for developing cancer. (Rock et al., 2018)

Multiple genetic and epigenetic alterations drive the malignant transformation of oral leukoplakia, and in fact some of the same genetic mutations and features of chromosomal instability observed in oral cancer have been observed in oral leukoplakia. (Villa & Woo, 2017) Table 3 shows several molecular markers seen in oral leukoplakia which have been studied.

MOLECULAR MARKERS
DNA aneuploidy
loss of heterozygosity
cell cycle, proliferation and apoptosis related molecules; e.g. Cyclin D
immortalisation; e.g. telomerase
angiogenesis; e.g. VEGF-A
cell adhesion; e.g. E-cadherin
MMPs (metalloproteinases); e.g. MMP 1, 2, 9, 12
inflammation; e.g. COX-2
signalling pathways; e.g. EGFR/TGF-α
epigenetic events, DNA hypermethylation; e.g. p16, p15, p14
epigenetic events, histone modifications; e.g. H3 (Lys4, Lys9, Lys18, Lys27, Lys36)
epigenetic events, altered expression of miRNAs; e.g. miR-21, -31, -146 a, -211…
stem cells; e.g. PDPN, ABCG2
DNA damage; e.g. γ-H2 AX, phospho-CHK2
S100 proteins; e.g. S100 A7
epithelial-to-mesenchymal transition; e.g. Snail and Axin2
salivary metabolomics; e.g. 1-methylhistidine, inositol 1,3,4-triphosphate

Table 3: Molecular markers in oral leukoplakia (Nikitakis et al., 2018; Zhang et al., 2017; Sridharan et al., 2019)

MEDICAL	SURGICAL
carotenoids e.g. beta-carotene, lycpene	conventional excision
vitamins e.g. retinoids, vitamin B, vitamin C	electrocoagulation
anti-neoplastic agents e.g. bleomycin	cryosurgery
polyphenols e.g. curcumin	laser surgery
photodynamic therapy	

Table 4: Medical and surgical treatment of oral leukoplakia (van der Waal, 2019; Villa & Woo, 2017; Deliverska, 2017)

The potential for molecular biomarkers to facilitate prediction of malignant transformation would be a major step in the guidance of clinical management, allowing the selection of the optimal individualised treatment based on the properties of lesions. (Nikitakis et al., 2018) However, despite the accumulating knowledge of the molecular basis of oral carcinogenesis, as of yet predictive markers are unable to predict malignant transformation of leukoplakia in a reliable and reproducible manner. (Deliverska, 2017; Nikitakis et al., 2018; Zhang et al., 2017) Therefore, histopathological examination to identify epithelial dysplasia remains the diagnostic gold standard, and management remains to be primarily guided by the histopathological examination coupled with the above mentioned factors. (Deliverska, 2017)

There are several treatment modalities for leukoplakia, including both medical and surgical methods. (Table 4)

All treatment begins with the elimination of risk factors; primarily tobacco cessation. (van der Waal, 2019; Deliverska, 2017) In the presence of epithelial dysplasia, surgical management of oral leukoplakia is recommended. In the absence of dysplasia, lesions may or may not be completely surgically removed. This decision should consider the clinical characteristics which determine the risk status of the lesion, including the site, size and clinical presentation as well as the patient's motivation for cessation of risk factors. (van der Waal, 2019; Villa & Woo, 2017; Deliverska, 2017)

Independent of the type of management, recurrences may occur, either in the same location or elsewhere in the oral cavity. Apart from this, none of the treatment modalities guarantee a reduction in the risk of malignant transformation. Therefore for all patients with leukoplakia, whether treated or untreated, lifelong follow up is recommended. (van der Waal, 2019; Deliverska, 2017)

When considering the 43-year-old patient presented in this report, the features of the oral leukoplakia indicate a low risk lesion in terms of it being a homogenous lesion, smaller than 200mm2 with no dysplasia.

However the lesion is in a high risk site; the floor of the mouth. Apart from this the patient is at a high risk for developing further oral leukoplakia lesions, oral epithelial dysplasia and oral squamous cell carcinoma due to his ongoing tobacco habit and a smoking history of 17 pack years.

Therefore, long-term and life-long recall appointments are essential in order to review not only the current lesions for any concerning changes, but also the rest of the oral cavity for the development of any early signs of possible malignancy.

CONCLUSION

Oral leukoplakia has been a continued subject of discussion in the past decades, in terms of its definition, diagnosis and management. This has lead to wide variation in management depending not solely on the severity of dysplasia and other risk factors mentioned in this paper, but also on the clinician's preference.

The lack of high-level evidence leaves uncertainty on how to best manage oral leukoplakia. Although current knowledge on predictive factors aids in the identification and management of high risk lesions, this is not a fail-safe method and malignant transformation can occur in any oral leukoplakia.

This highlights the need for developing a more thorough understanding of the critical molecular events driving the malignant transformation of oral leukoplakia. This would enhance the clinical decision making process, which is of particular importance in cases such as the one encountered in this case report, where although no epithelial dysplasia was detected, the lesion was still located in a high risk area.

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SURGICAL APPROACHES TO CLOSURE OF ORONASAL COMMUNICATIONS

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ABSTRACT

An oronasal communication is an uncommon presentation in the day to day dental practice. Etiological factors are numerous and could range from cleft palate, systemic and local infection, tooth extraction to post-surgical complications. A nineteen-year-old patient diagnosed with a recurrent juvenile nasopharyngeal angiofibroma located at the base of the skull presented for the closure of an oronasal communication, a direct consequence of the Weber-Ferguson Incision and Maxillary Swing Procedure used to access and excise the tumour. The patient complained of food trapping within the communication, hypernasality and bad odour. Primary closure through a palatal rotational flap was attempted, however full closure was not possible due to the anatomy of the location of the communication as well as the size of the communication.

This paper aims to explore the different surgical techniques available for closure of an oronasal communication that offers the least amount of comorbidity and that has the greatest success.

KEYWORDS

Oronasal communication, Surgical Closure, Palatal Flap.

INTRODUCTION

An oronasal communication (ONC) is a communication between the oral cavity and nasal cavity as a result of a breach through the hard and/or soft palate, an uncommon presentation in the day to day dental practice[1].

Etiological Factors can be separated into two main categories: Congenital or Acquired. The most common congenital factor is a cleft palate, where surgery for attempted primary closure tends to fail, and so resulting in a persistent ONC. Acquired defects are of multiple origins including, dental extraction, trauma, local or systemic infection, neoplasms as well as postoperative complications. Maxillary swing procedures to access the base of the skull and dental implant removal have all been described to cause ONCs[2].

Many tumours and cysts involving the maxilla, palate and surrounding structures could result in an ONC as a post-surgical complication or through pathological destruction. Figure 1 represents a list of proposed tumours that could result in an ONC when being surgically treated[3]. Communications can be classified according to their size: small (<2mm), medium (3-5mm) or large (>5mm). ONCs may also be classified according to their location. Namely, anterior; midpalatal; fistula at the junction between hard and soft palate or; soft palate fistula. If the communication lasts longer than 3 weeks, it is then referred to as a chronic communication[4].

In 2007, Smith et al devised a more reliable classification of communications of the palate titled 'Pittsburgh Fistula Classification System'. They describe and define an oronasal fistula as "patency between the oral and nasal cavities", regardless of its aetiology and functionality.

Therefore, this classification can also be adapted for classifying ONCs. The reason for devising a new classification was to solve the problem of an existing, reliable classification, that could be used globally that would make comparison of treatment methods easier and more reliable[5]. Figures 2 and 3 explain this in greater detail.

Clinical features depend on the size, location and cause of the ONC. Escape of liquids through the nose appears to be the most common symptom. Hypernasality, chronic sinusitis, recurrent infection, fetid odour and bad taste have also been described[2,3,6].

Treatment of an ONC may be done either surgically or non-surgically. A non-surgical approach involves the delivery of a prosthesis, 'an obturator', that seals the ONC from the oral cavity. Silicone buttons that occlude the communication orifice itself have also been used as alternatives to conventional obturators[7].

More commonly though, a surgical approach is used as definitive treatment. Communications larger than 5mm do not close spontaneously. Intra-oral surgical closure is difficult due to limited access, poor vision limited availability of surrounding tissue, scarring from previous surgery and poor flexibility and elasticity of neighbouring tissues. Palatal rotational flaps, tongue flaps, buccal fat pad flaps, free flaps, decellularized dermal grafting and V-Y flaps have all been described and executed in the literature for the closure of ONCs according to size and history of failed closure[2,7-12].

Tumours Involving the Palate	
Common	**Uncommon**
Squamous Cell Carcinoma	Squamous Papilloma
Basal Cell Carcinoma	Verrucous Carcinoma
Pleomorphic Adenoma	Verruciformxanthoma
Mucoepidermoid Carcinoma	Nasopharyngeal angiofibroma
Adenoid Cystic Carcinoma	Chondroma
Polymorphous low-grade carcinoma	Liposarcoma
Oral Haemangioma	Myoepithelioma
Oral Fibroma	Basal Cell Adenocarcinoma
Giant Cell Fibroma	Adenomatoid odontogenic tumour

Figure 1: Table listing proposed tumours involving the palate (Adapted from: Oronasal Fistula and Complete Edentulism: What to Do? By Kuar P. & Kuar J., 2008)

The Pittsburgh Fistula Classification	
Type of Fistula	**Location**
Type I	Uvula
Type II	Soft Palate
Type III	Junction between Hard and Soft Palate
Type IV	Hard Palate
Type V	Incisive Foramen
Type VI	Lingual-Alveolar
Type VII	Labial- Alveolar

Figure 2: Table Listing the Type of Fistula According To the Location. Adapted from The Pittsburgh Fistula Classification System: A Standardized Scheme for the Description of Palatal Fistulas, Smith et al, 2007.

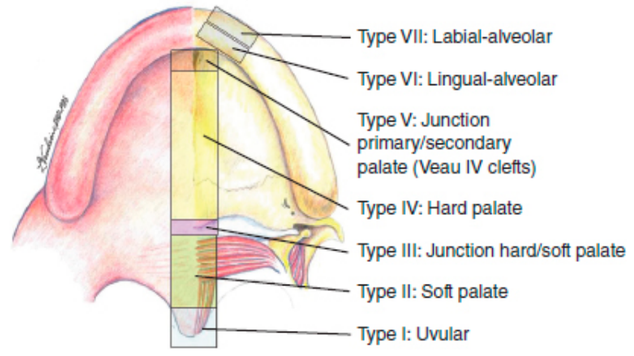

Figure 3: Diagram Annotating Type of Fistula and Location. Adapted from The Pittsburgh Fistula Classification System: A Standardized Scheme for the Description of Palatal Fistulas, Smith et al, 2007.

CASE PRESENTATION

A nineteen-year-old male presented to the University of Malta Dental Teaching Clinic upon referral from private practice for non-surgical closure of an ONC classified as large in size and at the junction between the hard palate (Fig 4.).

According to the Pittsburgh classification, this is a Type IV communication i.e within the hard palate.

The patient was diagnosed with a Recurrent Juvenile Nasopharyngeal angiofibroma at the age of fourteen. The patient also presented with paraesthesia around structures being supplied by the infraorbital nerve. Paraesthesia was the result of the Weber-Ferguson Incision used to access the tumour at the base of the skull that includes an incision just inferior to the infraorbital foramen.

The patient also presented with Grade 2 mobility on teeth 21 and Grade 1 mobility on tooth 22. Periapical dental radiographs of the area also showed associated bone loss around the mobile teeth.

The patient was complaining of bad taste and odour as well as food trapping within the communication and altered speech, mainly hypernasality.

The ONC occurred as a post-surgical complication following the excision of recurrent juvenile nasopharyngeal angiofibroma. Treatment for this tumour is through surgical excision. To access the tumour, elective surgery with a maxillary swing procedure through a Weber-Ferguson incision was performed over-seas under general anaesthesia. An initial treatment plan was non-surgical closure with the use of a removable prosthesis and obturator.

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However, upon follow-up overseas, the patient opted to undergo primary closure through surgery.

The attempted closure of the ONC was done via a routine palatal rotational flap and sutured. The patient presented to the clinic post-surgically for dental assessment and review of closure (Fig 5.). On re-examination, the ONC persisted albeit smaller in size. Evident scarring and mucosalization at the donor site were evident. The patient's previous complications were reduced, especially in regards to food trapping and altered speech.

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DISCUSSION

An oronasal communication (ONC) is a break in the hard or soft palate

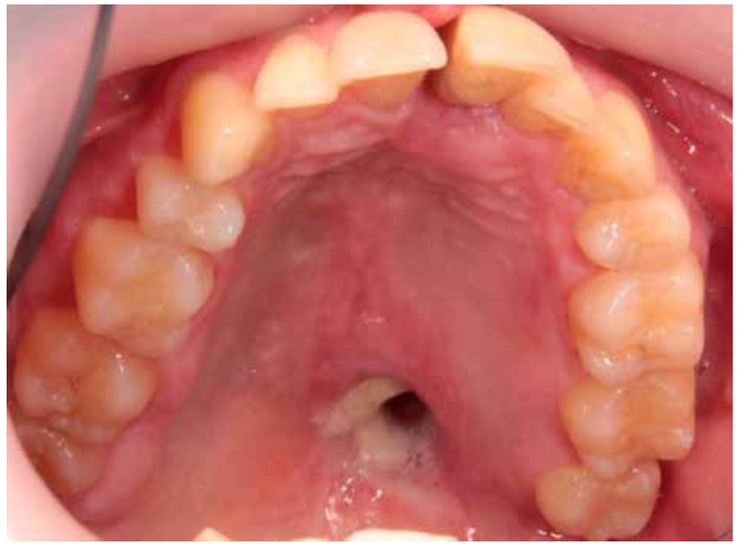

Figure 4: The Oronasal Communication at presentation

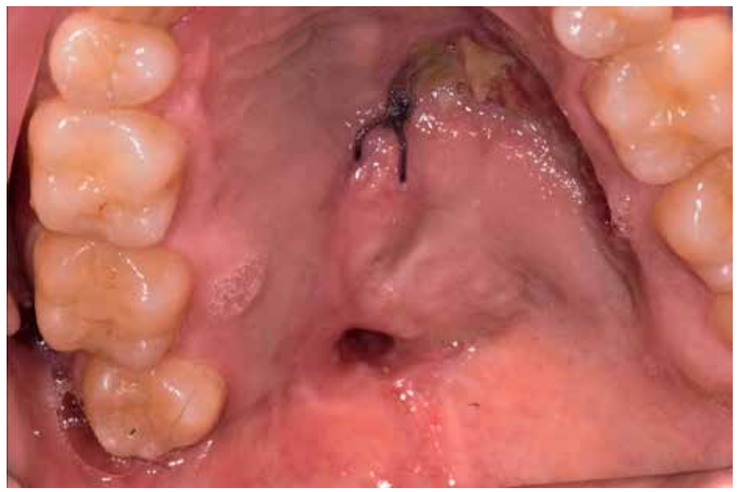

Figure 5: The Oronasal Communication post-attempted surgical closure with a palatal rotational flap

leading to a communication between the oral cavity and nasal cavity. The many aetiological factors can be divided into acquired and congenital.

Cleft palate is the most common congenital. Acquired aetiologies include trauma, local or systemic infection, dental extraction, implant removal and many surgical procedures that involve the maxilla, palate and other surrounding structures. The clinical features of ONC are food escaping through the nose, fetid odour, halitosis, hypernasality and defective speech[2].

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Recurrent Juvenile Nasopharyngeal angiofibroma is a rare but histologically benign tumour that is highly vascular and locally invasive and represents 0.05% to 1% of all tumours in the head and neck. The tumour presents as a swelling that originates at the sphenopalatine foramen that often causes nasal obstruction and repeated bleeding due to its great vascular supply.

The vascular nature of the tumour is also the reason as to why a biopsy is often not required, due to the excessive, uncontrollable bleeding. Diagnosis is often based on CT and MRI examination, with MRI being more favourable as the limits of the lesion are more evident and aid in planning surgery[13]. This tumour is much more common in males suggesting some relation to the male hormone, especially testosterone[13].

Often, elective surgical excision of the tumour is performed and is the first line of treatment. To access the skull base, a maxillary swing approach gives the best access and vision, often employing a Weber-Ferguson Excision. ONC is a common complication associated with the procedure[13] .Avoiding the midline incision intraorally may lessen the chances of the formation of the ONC[12]. This tumour has a very high recurrence rate, having been documented to be between 20% to 50%[13].

Many different techniques have been reported for surgical closure of ONCs. The most common of which seems to be a palatal flap procedure. Other methods of surgical closure have been reported in the literature. Tongue flaps, musculomucosal flap and the buccal artery musculomucosal flap are being used more frequently when palatal flaps, or approximation is not possible in inelastic areas such as the hard palate and when recurrent palatal flaps have failed due to dehiscence or poor vascular supply[9]. Palatal flaps may be straight advancement flaps or rotational flaps and are both based on the greater palatine artery. Rotational flaps seem to be of a greater advantage as they offer more mobility and flexibility when compared to straight advancement flaps. The flap must harbour a wide-enough base for adequate blood perfusion to the flap apex for successful healing and wound closure[14].

A great advantage of this type of flap is the ability of the defect to be covered in similar tissues that were present before the defect began. It has also been reported to have a 97% success rate, given that adequate blood supply is available to the flap.

These mucoperiosteal flaps still do not offer much elasticity, especially when larger ONCs ae present and so scarring is inevitable. Partial flap necrosis has also been documented[15]. Larger communications may also require more than one procedure for complete closure[2,4]. These findings coincide with the presentation of the patient upon second attendance to the clinic, post-closure surgery.

Scarring at the wound donor site was evident and complete closure was not possible. This is most likely due to the size of the ONC and the limited amount of palatal mucosa that was available in the area. Also, relieving incisions must be utilised with precaution in the hard palate so as not to interfere with the vascular supply to the wound and inadvertently lead to necrosis of the flap and no surgical closure of the ONC[15].

Tongue flaps first used in 1909 are a good substitute for palatal flaps due to the abundant vascularity, flexibility, elasticity and reduced scarring at the donor site. It has been reported to have a success rate between 85% to 95.5%[11]. There also appears to be less recurrence of ONC when the tongue flap is used[9]. The disadvantage with

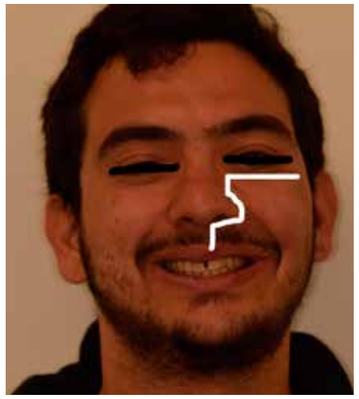

Figure 6: White line representing the Weber-Ferguson incision used to access the tumour through a Maxillary Swing procedure. Note the incision at or low the infraorbital, therefore directly severing the infraorbital nerve.

tongue flaps, however, is the need for a second surgery to detach the pedicle produced by most tongue flaps when acquiring the graft and patient consent given the comorbidities of potential function loss of the tongue such as poor masticatory ability and altered speech[16].

Cole et al have documented the success of using Alloderm, decellularized human dermis. This graft acts as a scaffold for host cells to infiltrate, especially fibroblasts. Epithelial reconolisation of the graft is quick. It has also been reported to be unidentifiable from untouched host mucosa 4 weeks post-surgery using the intramucosal sandwich technique where a layer of the alloderm is placed between the nasal respiratory mucosa on the floor of the nasal cavity and oral mucosa. The biggest advantage of this procedure is the reduced comorbidity to donor sites post-surgically[9].

Facial artery musculomucosal flaps (FAMM) incorporating mucosa, submucosa, facial artery and buccinator has also been reported in the literature and first used in 1991 for intra-oral defects including the palate. A pedicled FAMM flap has been described by Joshi et al for a palatal defect resembling the patient mentioned above to great access with little comorbidity[8]. Ideally, a two-layered flap is used i.e. a layer to close the nasal aspect of the communication and a second layer to close to the oral aspect of the ONC. It has been reported that closing ONCs in their procedure can result in a 100% success rate. Using respiratory or oral mucosa in a hinge-flap method to close the nasal layer and a mucoperiosteal flap to close the oral cavity has been reported 10.

Soft palate breaches are closed through the approximation of flaps through the use of split-thickness incision and approximation of the edges of the ONC at mucosal and submucosal level[2].

CONCLUSION

An oronasal communication is a breach in the hard or soft palate leading to a communication between the oral cavity and nasal cavity, an uncommon presentation in the dental practice.

The low frequency of cases of oronasal communication seen by oral surgeons may explain the lack of information and literature that is currently available. A study coming from the University of Campinas, in Sao Paolo, Brazil reviewed different treatment methods for oroantral and oronasal communications.

Out of the 112 participants, only 11 patients presented with oronasal communications[14]. Oral Surgeons not exposed frequently to the surgical closure of oronasal communications might not be well practised in the surgical skill required for effective treatment. The case that was seen at the Teaching Clinic involved a nineteen-year-old presenting with an Oronasal Communication following the excision of a recurrent nasopharyngeal angiofibroma at the base of the skull.

The communication can be described as large, and at the posterior border of the hard palate. The anatomy of the location and mucosa available for a palatal rotational flap has poor elasticity and flap breakdown has also been documented.

Other procedures could have benefited the patient such as a pedicled tongue flap, that may have been more effective with a large communication such as this one. There is a need for further study regarding oronasal communications and surgical closure. Such study would assist surgeons in making decisions on the type of surgical procedure needed with respect to the size and location of the oronasal communication at hand.

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PLANNING FOR YOUR FUTURE FINANCIAL CUSHION

By Joanna Azzopardi

Insurance & Pensions Manager,
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Retirement planning is important for everyone regardless of education and wealth. No matter how young at heart we may feel, the truth is that one day we will have to leave the working world and start to enjoy our retirement. Life expectancy is constantly increasing, thanks to the advancement in healthcare and medical science. This means that our life in retirement is also becoming longer and therefore the need to build a financial cushion is now crucial.

At retirement, our employment income will be replaced by the state pension which is capped at a maximum. For us to be able to enjoy the same standard of living we will need additional income, or we will have to drawdown money from the savings we would have accumulated throughout the years.

Individuals are generally faced by an unpleasant surprise when reaching retirement age, as it is only then when they realise that the state pension benefit is much lower than their income during employment. Since the state pension is capped, the shortfall experienced by high income earners is much greater than for others.

Private pension plans were introduced in Malta in 2015. Individuals who choose to contribute into a pension plan may benefit from a tax credit of 25% on their contribution. These qualifying pension schemes specifically provide an attractive tax incentive to encourage individuals to save for the future. An individual who would have contributed €3,000 in 2022 will receive a tax credit of €750 in 2023. This means that the cost of saving €250 per month/ €3,000 per year is essentially €2,250, because €750 will be credited to the individual's tax bill the following year. These plans usually start from a minimum of €40 per month and being a long-term product, one should choose an amount that is affordable to continue to save until retirement date.

There are different types of personal pension plans which include 'With-Profits' or 'Unit-Linked'. The main difference between the two is the investment element i.e., where the pension contributions are invested. 'With-Profits' plans have contributions pooled together with money from other policyholders and invested in the insurance Company's with-profits fund. This fund is highly diversified and cautious and seeks to provide smooth and stable returns.

'Unit-Linked' plans provide a more adventurous approach where the contributions buy units in a selection of funds of the individual's choice. Here the individual has more control and the return on investment depends on the performance of the funds to which the plan is linked. These plans usually have a higher risk/ reward profile than with-profits.

Saving an affordable amount in a pension plan over a long period of time and staying invested to benefit from the power of compounding will help grow one's wealth exponentially.

The substantial pension pot may be accessed when the individual reaches the age of between 61 and 70 years, depending on the retirement date selected by the individual. On retirement date, the individual may take 30% of the pension pot as a tax-free lump sum and the remaining 70% will have to provide regular income, either in the form of an 'Annuity' or 'Programmed Withdrawals'.

When you are young you are in the best position you will ever be in to start planning for your retirement. It might feel strange to think about retiring when you would have just started a career, however saving a little amount early can have a major impact on your savings in the future. As Albert Einstein once said 'Compound Interest is the eighth wonder of the world. He who understands it, earns it...he who doesn't… pays it!'

For further information, kindly contact Jesmond Mizzi Financial Advisors Ltd on: insurance@jesmondmizzi.com or on (+365) 2343 5715

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[1] Tiba A et al., Journal of American Dental Association, 144(10), 1182-1183,2013.
[2] based on sales figures

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