Necrotising migratory erythema leading to the diagnosis of a metastatic glucagonoma without diabetes

By

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2016395929

Submitted in fulfilment of the requirements in respect of the Master's Degree MMed

in the

Department of Internal Medicine

Faculty of Health Sciences

University of the Free State

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Published on 05/08/2020: Journal of Endocrinology, Metabolism and Diabetes of South Africa (JEMDSA).

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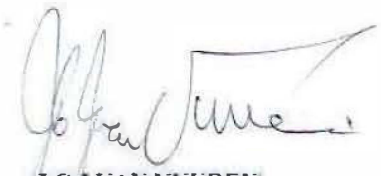

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Abstract

A case of necrotising migratory erythema (NME), which is one of the distinctive paraneoplastic skin manifestations associated with the glucagonoma syndrome, is described and discussed. In 80% of all patients with glucagonoma, NME is the first clinical sign. The glucagonoma syndrome is a constellation of clinical features: NME, weight loss, anaemia, diabetes, diarrhoea, thromboembolism and neuropsychiatric symptoms. The global incidence of glucagonoma is one in 20 million people per year. The male to female ratio is 0.8:1 with the mean age of diagnosis being 52.2 years. The median time in relation to the initial onset of symptoms and the correct diagnosis is 3.5 years. The 10-year survival rate in patients with metastatic disease is 51.6% and without metastatic disease 64.3%. SPECT scan has a sensitivity range of 67–100% for detecting neuroendocrine tumours. Differential diagnoses of other skin conditions that mimic NME are: bullous pemphigoid, vasculitis, acrodermatitis enteropathica, chronic mucocutaneous candidiasis, seborrhoeic dermatitis, contact dermatitis, pellagra, inflammatory bowel disease, liver cirrhosis, coeliac disease, chemical burns, eczema, herpes etc. A satisfactory response to somatostatin as medical therapy in a case-study patient with metastatic disease is reported.

Keywords

Glucagon

Glucagonoma

Necrotising migratory erythema

Skin

Rash

Neuroendocrine

Octeotide

SPECT

Somatostatin

Diarrhoea

Pulmonary embolus

Venous thromboembolism

Diabetes

Zinc

Abbreviations

NME – Necrotising Migratory Erythema

KG – Kilogram

CT – Computerised Tomography

SPECT – Single Photon Emission Computerised Tomography

WHO – World Health Organisation

MEN – Multiple Endocrine Neoplasia

GCA – Glucagon Cell Adenomatosis

GCGR – Glucagon receptor

MTOR – Mammalian Target Of Rapamycin

PRRT – Peptide Receptor Radioligand Therapy

GLP – Glucagon Like Peptide

Chapter 1

1.1. Clinical Presentation

A 54 year old woman presented with two years duration of diarrhoea. It was accompanied with a four month history of a diffuse skin rash which caused severe discomfort. She also complained of decreased appetite and weight loss, quantified as 39kg over the period of a year. Further medical history revealed she had an existing diagnosis of hypothyroidism on thyroid hormone replacement therapy as well as prior therapy with antibiotics and corticosteroids. There was no significant family history, a 27 pack year smoking history and did not consume alcohol.

The findings on physical examination revealed an erythematous, scaly skin rash with areas of crusting. These lesions were distributed on her sub-mammary folds, anterior surfaces of her upper and lower limbs, abdomen and groin (Figure A). There were areas of healing skin lesions with brownish-bronze hyperpigmention, dry mucosal surfaces, conjunctival pallor and excessive skin folds. Abdominal examination revealed a soft non-tender hepatomegaly. The clinical assessment made by the dermatologist was Necrotising Migratory Erythema (NME) secondary to a glucagonoma. This prompted further investigation in the form of blood tests, imaging studies and histological assessment.

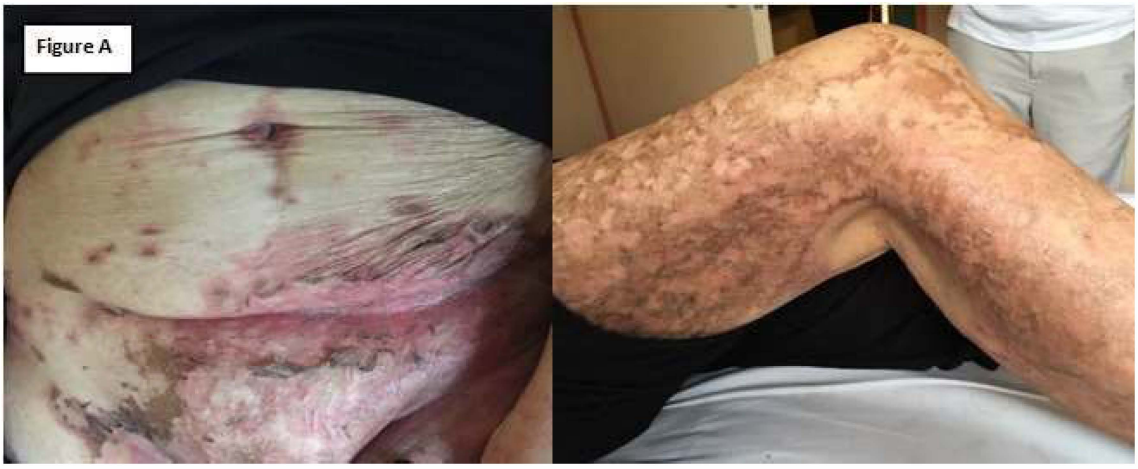

Figure A: Image shows clinical appearance of Necrotising migratory erythema (NME) involving abdomen, groin and lower limb.

1.2. Investigations

The blood results showed low haemoglobin of 10.7g/dL, hyponatraemia (132mmol/L) with normal urea and creatinine. The liver function tests were deranged: low serum total protein of 55g/L, low serum albumin of 23g/L, normal gammagluteryl transferase of 43U/L and raised alkaline phosphatase of 118U/L. Other tests demonstrated a normal alpha-feto-protein of 3.2ug/L, normal random blood glucose of 3.6mmol/L, normal glycated haemoglobin of 5%, raised lactate dehydrogenase of 221U/L, raised C-reactive protein of 96mg/L and negative syphilis serology.

The imaging studies performed were Computerised Tomography (CT) and Single Photon Emission Computerised Tomography (SPECT) scans. Abdominal CT scan found a large heterogeneous mass affecting segments eight and five of the liver, measuring 114mm in diameter. Multiple sclerotic lesions were seen in vertebrae, pelvis and proximal femurs which were in keeping with metastasis. The pancreas was reported to have a normal homogenous appearance with no masses. SPECT with OctreoScan showed focal increased uptake in the head of the pancreas. There were also multiple areas of uptake in the liver (Figure B), axial and appendicular skeleton in-keeping with metastasic disease.

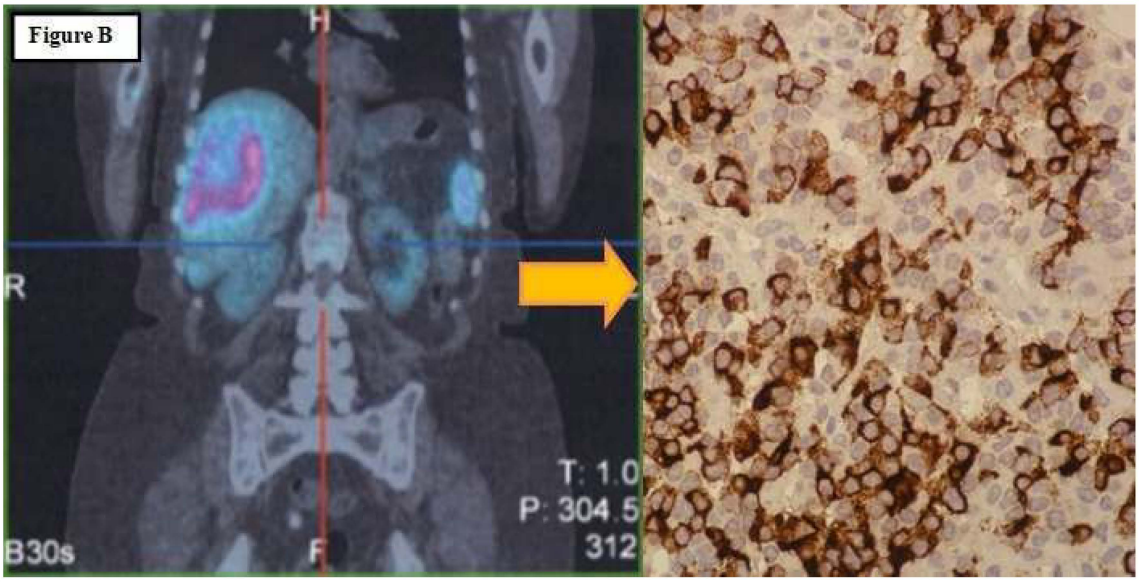

Figure B: Image on left shows Single Photon Emission Computerised Tomography (SPECT) with high somatostatin uptake as "hot spots" in liver shown in purple. Image on right shows histology of liver biopsy taken from purple area of high uptake using a monoclonal antibody to stain for glucagon.

The histology report of a skin biopsy showed: hyperkeratosis, a spongiotic reaction pattern with eosinophils and intraepidermal vesicles. Immunohistochemical stains on skin biopsy excluded pemphigus. The liver biopsy revealed atypical cells with a nested pattern of monomorphic tumour cells which had showed a salt and pepper chromatin. The immunohistochemical stains on liver biopsy confirmed a metastatic neuroendocrine tumour of pancreatic origin. Further immunohistochemical testing (Figure B) was performed using a monoclonal antibody specifically for glucagon. This confirmed the diagnosis of a metastatic glucagonoma.

1.3. Management

Our patient's nutritional status had improved by administration of zinc and dietary protein supplementation. This resulted in improvement of the skin rash.

The liver and bone metastasis precluded primary surgical resection and hence the primary treatment regimen chosen for this patient was medical. Subcutaneous octreotide injections were used to reduce the secretion of glucagon. The patient was followed up at intervals of one month, six months and eighteen months. At the initial follow up, the skin rash had regressed (Figure C) and diarrhoea had resolved. The sixth month follow up clinical examination revealed that all skin lesions had healed completely.

Eighteen months later, the patient was admitted for investigation of poor effort tolerance and dyspnoea. Findings on clinical examination recorded were tachycardia, tachypnoea and normal blood pressure. A CT pulmonary angiogram confirmed multiple pulmonary emboli and anticoagulation therapy was instituted. Her weight had increased by 18kg from the initial admission weight. A SPECT with OctreoScan was repeated and it showed: no new lesions and reduced activity of the previously seen skeletal lesions. We appreciated this as a positive response to medical therapy.

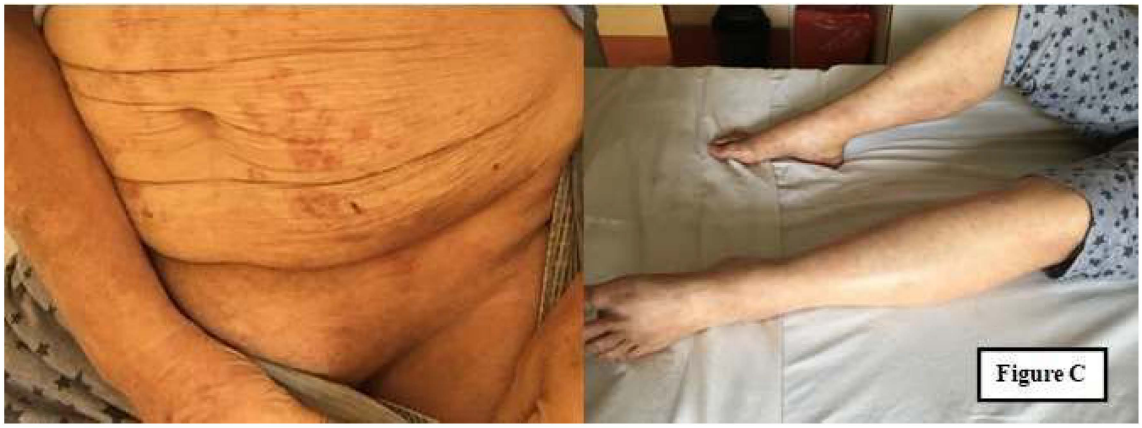

Figure C: Image on left shows healed Necrotising migratory erythema (NME) in the groin. Image on right shows healed NME involving lower limbs.

1.4. Discussion

A glucagonoma is a neuroendocrine tumour of pancreatic origin (1). Other neuroendocrine tumours are insulinoma, gastrinoma, vipoma and somatostatinoma (2)(3). These tumours can be classified as either functional or non-functional according to the WHO classification of endocrine tumours (2)(4). Functional tumours produce a clinical syndrome due to the production and release of associated hormones (2).

When a neuroendrocrine tumour produces large amounts of glucagon, it is called a glucagonoma. If a glucagonoma is functional, a glucagonoma syndrome may be present. The glucagonoma syndrome typically is a constellation of clinical features: NME, weight loss, anaemia, and diabetes (5). Additional clinical features include: diarrhoea, thromboembolism which was present in this patient and neuropsychiatric symptoms which were not present. The biologically active form of glucagon is 3500 Daltons (6). Some tumours produce biologically inactive forms of glucagon which do not have any clinical effect. The secretion of biologically active fractions of glucagon is responsible for the above clinical features (6).

NME is one of the distinctive paraneoplastic skin manifestations associated with the glucagonoma syndrome (7). This rare condition presents with a very specific constellation of features. A prompt and accurate diagnosis can be made if the treating physician is aware of these features (1). Patients may present to physicians in a number of ways: new onset

diabetes, weight loss, anaemia or to a dermatologist for a skin rash years before being correctly diagnosed. The median time in relation to the initial onset of symptoms and the correct diagnosis is 3.5years (8).

1.4.1. Incidence

The global incidence of glucagonoma is one in twenty million people per year (1)(9). The male to female ratio is 0.8:1 with the mean age of diagnosis being 52.2 years (10). The average size of the pancreatic mass at the time of diagnosis is 5cm in diameter (10). In 80% of all patients with glucagonoma, NME is the first clinical sign (10). Approximately 50% of all cases are diagnosed after metastasis have occurred (6). The 10 year survival rate in patients with metastatic disease is 51.6% and 64.3% without metastatic disease (5).

1.4.2. Pathophysiology

The pancreas is an endocrine and exocrine organ (11,12). The endocrine pancreas consists of functional units called Islets of Langerhans which contain: alpha cells that secrete glucagon, beta cells that produce insulin, delta cells that produce somatostatin, pancreatic polypeptide cells that produce pancreatic polypeptide and epsilon cells that produce ghrelin(11). The exocrine pancreas consists of acini and ductal cells. Acini produce digestive enzymes: trypsin, chymotrypsin and pancreatic lipase whilst ductal cells produce bicarbonate (12).

Glucagon is secreted as proglucagon which consists of 178 amino acids as a protective response to prevent hypoglycaemia (8)(13)(14). The primary site of action is in the liver where glucagon stimulates gluconeogenesis and glycogenolysis (6,7). Gluconeogenesis is the formation of glucose from the breakdown of amino acids and lipids. This process is consumptive and results in a deficient caloric state. High glucagon levels are implicated in the pathogenesis of NME.

Other molecules related to proglucagon are glucagon-like peptide 1 (GLP-1) and glucagon-like peptide 2 (GLP-2). Many of the novel diabetic drugs are based on the physiology of these molecules. These new drugs are effective at lowering serum glucose levels and as a consequence also lower glycated haemoglobin levels. GLP-1 receptor agonists and

dipeptylpeptidase-4 (DPP4) inhibitors are examples of these drugs. These drugs raise the serum concentration of GLP-1 which result in a reduction in desire for food ingestion, loss of body weight, improved insulin production, increase in insulin sensitivity, reduction in hepatic glucose production and increased uptake of glucose into skeletal muscle(15). Specific parts of the brain have been identified as having receptors to GLP-1 thus leading to these effects. These parts of the brain are the paraventricular and arcuate nuclei(16).

Glicentin is another newly discovered peptide under investigation that is formed from proglucagon. Glicentin contains 69 amino acids and contains glucagon within that chain of amino acids(14). The secretion of glicentin is stimulated by the presence of digested food in the duodenum. Glicentin promotes intestinal mucosa proliferation, reduces the rate of bacterial translocation, reduces gastric acid secretion and reduces intestinal motility, The laboratory test to measure glicentin is an enzyme-linked immunosorbent assay which is commercially available. Higher glicentin levels have been found in patients with chronic kidney disease suggesting a renal mechanism of excretion(14). Obese patients have lower glicentin levels whilst patients post bariatric surgery have an increase in glicentin levels post surgery(14). The clinical relevance of this peptide has not been fully elucidated and further research is underway.

There has been suggestion that there is a link between a family history of Multiple Endocrine Neoplasia (MEN) type 1, Von Hippel Lindau disease and glucagonoma however no genetic factors have been conclusively found(6)(17)(18). Currently research into the genetic cause of glucagon producing tumours is underway. There has been a study looking at the genotype in six patients with high glucagon levels. One such receptor identified is the glucagon receptor (GCGR). Studies in mice have shown that abnormalities in the glucagon receptor can lead to hyperglucagonemia and alpha cell hyperplasia(18). It is proposed that this alpha cell hyperplasia may the first step towards an established malignancy such as glucagonoma. The P86S mutation in the glucagon receptor was newly discovered by Zhou et al. This is a down regulating or inactivating mutation which results a higher concentration of serum glucagon to achieve stimulation of the receptor. In order to produce higher quantities of glucagon, the Islet cells undergo a process of hypertrophy thus increasing the mass of Islet cells. It is during this state of continuous demand and hypertrophy that malignancy is thought to develop.

Homozygous mutations in glucagon receptors are more likely to result in disease as shown by Sipos et al. Heterozygous mutations are less likely to lead to disease since the normal allele compensates for the abnormal allele.

NME is a cutaneous, paraneoplastic manifestation which occurs as a result of longstanding high glucagon levels (13). High glucagon levels with diarrhoea lead to consumption and loss of nutrients. The chronic diarrhoea leads to malabsorption and deficiency of zinc and other essential fatty acids and minerals (7,9,19).A hypothesis regarding the aetiology of NME explains that the direct effect of glucagon on the skin leads to increased arachidonic acid formation in the skin(13). Due to the increased level of arachidonic acid, the inflammatory cascade is activated by friction in the intertrigenous areas (13). This may explain why some patients experience transient relief with corticosteroids. Skin lesions start as areas of erythema that proceed to become necrotic, blister, rupture and heal in the centre with hyperpigmentation typically bronze in colour (7). Crusting develops after blistering. Areas constantly exposed to friction such as the groin or feet may constantly weep (6). The histological findings are superficial epithelial necrosis, parakeratosis, spongiosis and subcorneal pustules or vesicles (20). In this case, the patient had a low total serum protein and low serum albumin which supported this deficient state. Other associated signs such as: glossitis, cheilitis and brittle crumbling nails can also occur due to this deficient state (7).

Functional glucagonomas are generally slow growing which often results in delayed diagnosis of a mass hence they are more likely to metastasise (4,21). Non-functional tumours generally grow to larger sizes and often develop areas of necrosis and cystic degeneration hence they are usually detected earlier before metastasis have occurred (3).

1.4.3. Imaging

In this case, the pancreas was found to have a normal appearance on CT scan. This is unusual because there were already large tumour metastasis in the liver. Neuroendocrine tumours identified on initial arterial phase CT range from only 55 to 60% (3).

SPECT scan has a sensitivity range of 67 to 100% for detecting neuroendocrine tumours (20). During a SPECT scan, a radio-labelled isotope of somatostatin is used so that areas with high concentrations of somatostatin receptors are detected as "hot spots" with gamma camera imaging (Figure B). The most common sites for metastasis are the liver (80.5%), peripancreatic lymph nodes (33.1%), bone (7.8%), mesentery or peritoneum (3.4%), lung (2%), spleen (2%) and adrenal gland (1.4%) (10). In the majority of cases described in the literature, lesions are found in the tail of the pancreas (10), however, in this case the Octreoscan detected high uptake in the head of the pancreas.

1.4.4. Differential Diagnoses

Initially the differential diagnoses considered in this case were that of an unknown primary where radiological investigations revealed metastasis without a visible primary, as seen on the CT scan. Tumours that metastasise with an unidentified primary other than neuroendocrine tumours include melanomas, lymphomas, sarcomas and carcinomas which may originate from lung, colon, breast, pancreas and stomach (22).

Glucagon Cell Adenomatosis (GCA) should also be considered when features of glucagonoma syndrome are found together with a normal pancreas on CT scan. This is a benign condition where the alpha cell populations of the pancreas becomes hypertrophied and excessive amounts of glucagon are produced in a generalised manner without mass formation (23). In our patient, GCA was excluded due to metastasis in the liver and bone, proving a malignancy.

A differential diagnosis of other skin conditions that mimic NME are: pemphigoid, vasculitis, acrodermatitis enteropathica, chronic mucocutaneous candidiasis, seborrhoeic dermatitis, contact dermatitis, pellagra, inflammatory bowel disease, liver cirrhosis, celiac disease, chemical burns, eczema and herpes (6). The skin biopsy performed on this patient was non-specific but excluded other pathologies.

1.4.5. Complications of Glucagonoma syndrome

The complications of a glucagonoma may be due to local direct extension of the tumour, a consequence of high glucagon levels or paraneoplastic.

Local complications include physical compression of the porta hepatis and surrounding bowel or vascular structures as the tumour increases in size and produces mass effect (3).This is more commonly seen in non-functional tumours which grow to larger sizes (3).

Functional tumours typically result in complications related to high glucagon levels. These are malnutrition, anaemia, diabetes , and secondary infection of NME skin lesions leading to systemic sepsis (23). In this case diabetes was excluded by normal fasting blood glucose and normal glycosylated haemoglobin. Only 40% of patients present with diabetes at the onset of symptoms, however 90% of patients develop diabetes with disease progression (8). Patients who develop diabetes secondary to glucagonoma are also at risk of macro and micro vascular complications from secondary diabetes mellitus. This patient did not have fasting hyperglycaemia at initial presentation nor at follow up visits. This may be due to a sufficient supply of endogenous insulin to counteract glucagon or up regulation of receptors resulting in glucagon resistance.

Paraneoplastic phenomena include vascular and neuropsychiatric symptoms. Deep venous thrombosis is a vascular paraneoplastic complication and is a frequent association in 10 -30% of patients with glucagonoma (24)(7). In patients with glucagonoma, the cause of death related to embolism is as high as 50% (7). This patient had no reported symptoms of venous thrombosis at the time of presentation, however during follow up, she was diagnosed with a pulmonary embolus. This highlights the importance of prophylactic anticoagulation due to the high associated mortality.

Neuropsychiatric symptoms are reported in 20% of patients (5). NME is a disfiguring skin disease that creates a high level of discomfort and psychological stress. These accompanied with hormonal and nutritional imbalances may lead to the development of neuropsychiatric

symptoms. The associated conditions are: dementia, major depressive disorder, psychosis, agitation, paranoid delusions, ataxia and hyperreflexia (21)(6). These neuropsychiatric conditions have been reported to improve once adequate treatment is initiated (21).

1.4.5. Management

The management of glucagonoma syndrome is a dichotomy between medical and surgical management. Metastatic disease is generally treated medically with some exceptions. All patients will require immediate medical optimisation regardless of final approach taken. This includes nutritional optimisation by a dietician, correction of electrolytes, rehydration and micronutrient supplementation such as zinc (19).

Surgical approaches include pancreaticoduodenectomy, distal pancreatectomy or enucleation of small lesions (3). Surgical resection is potentially curative in the absence of metastasis (3). Metastases are not an absolute contraindication to surgery. Tumour debulking or enucleation can be considered to reduce mass effect and to reduce amount of circulating glucagon hormone to palliate symptoms (3).

Medical therapy is the option of choice for the majority of patients with metastatic disease (21). Medical options include chemotherapy (4,6), trans-arterial chemo-embolisation (4), direct radiation therapy to liver and pancreas (5,10), radiofrequency ablations (9), cryoablation (3), biological therapy (1,9,21,25) and hormonal therapy with somatostatin (4,17,24). Somatostatin analogues have a consistently favourable effect in symptom amelioration (8)(3). Somatostatin's primary effect is inhibiting growth hormone as part of the negative feedback system. The secondary effect of Somatostatin is an inhibitory effect on both alpha and beta cells of the pancreas. This results in lowering of insulin and glucagon due to decreased secretion via hormonal inhibition (8). The adverse effects of somatostatin analogues include hypothyroidism, cholelithiasis, dysglycaemia, and bradycardia.

Chemotherapy using streptozotocin, 5-fluorouracil, cyclophosphamide, vincristine and tubericidin have been used with poor results (6). Biological therapy includes drugs such as

Sunitinib which is a multi-targeted tyrosine kinase inhibitor (inhibits vascular endothelial growth factor and platelet derived growth factor signalling (25)) and Everolimus which is an mTOR serine-threonine kinase inhibitor. Trans-arterial chemo-embolisation, direct radiation therapy to liver and pancreas, radiofrequency ablation and cryoablation are modalities that are used debulk liver or pancreatic lesions as a means of palliation (3)(26). A more recent novel treatment modality is Peptide Receptor Radioligand Therapy (PRRT) (4). Eldor et al (2011) has shown mixed results in their six patient cohort, thus more research is required regarding the efficacy of this new modality.

1.5. Conclusion

Glucagonoma remains a diagnostic challenge. In this case, we had the rare opportunity of diagnosing a metastatic glucagonoma that presented with NME and chronic diarrhoea. The decision to use primary medical therapy (somatostatin) was based on the fact that our patient had established metastatic disease. The response to treatment was satisfactory as evidenced by the resolution of NME and follow-up SPECT confirming reduced tumour activity and size. The mortality rate is unclear in this group of patients undergoing medical therapy with somatostatin who are not amenable to primary resection. This patient demonstrated the unfortunate delay in diagnosis due to low index of suspicion for the disease. Serum glucagon levels were not confirmatory whereas histological diagnosis was confirmed with immunohistochemical staining. We suggest that patients receive prophylactic anticoagulation once the diagnosis of glucagonoma has been confirmed due to the increased risk for and the high mortality associated with pulmonary embolism. While patients diagnosed before metastasis can be cured surgically, medical therapy can still offer a good quality of life in the event of metastasis, as demonstrated in this case.

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Chapter 2 – Published Article

Necrotising migratory erythema leading to the diagnosis of a metastatic glucagonoma without diabetes

A 54 year old woman presented with a four month history of a diffuse skin rash which did not respond to oral corticosteroids prescribed by a dermatologist. She also complained of diarrhoea, loss of appetite and weight loss of 39kg over a year. She had a 27 pack year smoking history, and was on thyroid hormone replacement therapy. There was no significant family history of any medical conditions.

She had an erythematous, scaly skin rash with areas of crusting, distributed on her sub-mammary folds, anterior surfaces of her upper and lower limbs, abdomen and groin with areas of healing skin lesions characterised by brownish-bronze hyperpigmention (Figure A). Her mucosal surfaces were dry and she had conjunctival pallor. She had normal blood glucose but was anaemic with haemoglobin of 10.7g/dL.

On abdominal Computerised Tomography (CT) scan there was a large heterogeneous mass in the liver and multiple sclerotic lesions in vertebrae, pelvis and proximal femurs in keeping with metastatic foci. Single Photon Emission Computerised Tomography (SPECT) with OctreoScan (octreotide uptake scan) had focal increased areas of uptake in the head of the pancreas consistent with a glucagonoma and increased uptake in the liver as well as skeletal metastases. The immunohistochemical stains on liver biopsy showed metastatic neuroendocrine tumour cells. Confirmation using a monoclonal antibody stain specifically for glucagon confirmed a glucagonoma. Serum glucagon levels were unavailable at the laboratory.

Our diagnosis was a metastatic glucagonoma presenting with Necrotising Migratory Erythema (NME).

NME is a cutaneous, paraneoplastic manifestation due to longstanding high glucagon levels[1] causing diarrhoea as well as malabsorption with deficiency of zinc and other essential fatty acids and minerals [2,3]. Excess glucagon leads to increased arachidonic acid formation in the skin[1]. Friction in the intertrigenous areas causes activation of the inflammatory cascade [1]. A differential diagnosis includes: bullous pemphigoid, vasculitis, acrodermatitis enteropathica, chronic mucocutaneous candidiasis, seborrhoeic dermatitis, contact dermatitis, pellagra, inflammatory bowel disease, liver cirrhosis, celiac disease, chemical burns, eczema, herpes, etc [4].

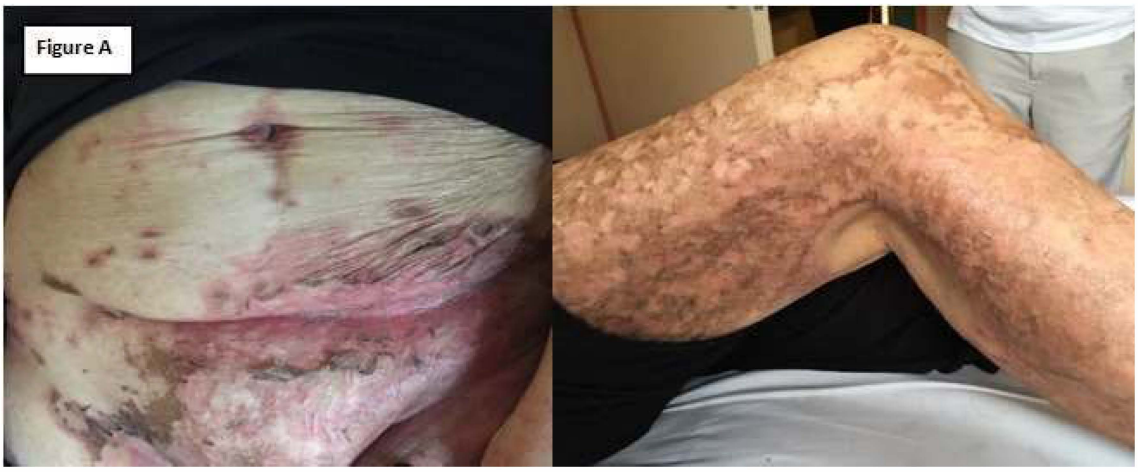

Figure A: Image on left shows clinical appearance of Necrotising migratory erythema (NME) involving abdomen and groin, image on right shows NME involving the lower limb.

The global incidence of glucagonoma is one in twenty million people per year [5]. A functional glucagonoma presents with a glucagonoma syndrome: NME, weight loss, anaemia, and diabetes [6], however all features may not be present concomitantly. Additional clinical features may include diarrhoea, thromboembolism and neuropsychiatric symptoms.

Our patient was treated with zinc (50mg eight hourly per os) and dietary protein supplementation (Fresubin®) on which the skin improved. She was then started on intramuscular octreotide injections (Sandostatin® LAR 20mg IMI monthly).

At the initial follow up, random glucose was still normal, the skin rash and diarrhoea had resolved. Follow up SPECT was done at 12 months (no progression) 18 months (no progression) and two years (evidence of progression). Eighteen months after diagnosis, the patient presented with a CT Pulmonary Angiogram confirmed pulmonary embolus.

With this case presentation we want to highlight NME as a paraneoplastic phenomenon of a functional glucagonoma that presented without diabetes. Prophylactic anticoagulation should be considered once the diagnosis of glucagonoma has been confirmed due to the increased risk and the high mortality associated with pulmonary embolism. Although patients diagnosed before the onset of metastatic disease may be cured surgically, medical therapy can still offer a good quality of life in the event of metastatic disease, as demonstrated in this case.

References:

1. E.A. M, P.R. C. Iatrogenic necrolytic migratory erythema: A case report and review of nonglucagonoma-associated necrolytic migratory erythema. J Am Acad Dermatol. 1998;38(5 II):866–73.
2. Tremblay C, Marcil I. Necrolytic migratory erythema: A forgotten paraneoplastic condition. J Cutan Med Surg. 2017;21(6):559–61.
3. Teixeira RC, Nico MMS, Ghideti AC. Necrolytic migratory erythema associated with glucagonoma: a report of 2 cases. Clinics. 2008;63(2):267–70.
4. Stacpoole PW. The glucagonoma syndrome: Clinical features, diagnosis, and treatment. Endocr Rev. 1981;2(3):347–61.
5. Al-Faouri A, Ajarma K, Alghazawi S, Al-Rawabdeh S, Zayadeen A. Glucagonoma and Glucagonoma Syndrome: A Case Report with Review of Recent Advances in Management. Case Rep Surg. 2016;2016(Figure 4):1484089.
6. Remes-Troche JM, García-de-Acevedo B, Zuñiga-Varga J, Avila-Funes A, Orozco-Topete R. Necrolytic migratory erythema: A cutaneous clue to glucagonoma syndrome. J Eur Acad Dermatology Venereol. 2004;18(5):591–5.

Appendices

Permission from 3 Military Hospital

Consent form signed by patient

Ethics approval letter

Documents submitted to UFS HSREC for ethics approval of a case report – equivalent to protocol

Turnitin

Author submission guidelines for JEMDSA

Published article as in Journal of Endocrinology, Metabolism and Diabetes South Africa (JEMDSA)

Dr Rahm Makan
Internal Medicine
University of Free State

To Dr LC Fosa
Head of Clinical Services
3 Military Hospital

Re: Request for permission of use of patient information

I am a medical registrar in Internal Medicine. During my rotation at 3 Military Hospital, I encountered a case that is suitable for my MMED dissertation as well as publication in a medical journal.

The patients details are: Mrs Christa Janse Van Rensburg
IMS no 77542330
Date of Birth 12/10/2017
Diagnosis: Metastatic Glucagonoma

I received written permission from the patient to use her information and images.

Will you please grant permission to use information from 3 Military Hospital to enable me to get ethics clearance.

Yours Sincerely

Rahm Makan

Cell: 072 144 6149
Email: rahm@live.co.za

APPROVED
LT COL LC. FOSA
83003988PE

CONFIDENTIAL

3MII/C//

Telephone: (051) 402 2375
Facsimile: (051) 402 2375
Enquiries: Lt Col JCJ van Vuuren

3 Military Hospital
Private Bag X40003
Brandhof
9324

2 August 2017

Lt Col LC Fosa

Re: Permission to use information from an individual patient

Please see the attached request from dr Makan. The patient agreed to her information being used. We need your permission to get this past the ethics committee.

Yours sincerely

(J.C.J VAN VUUREN)
PRINCIPAL SPECIALIST: INTERNAL MEDICINE: 3 MILITARY HOSPITAL: LT COL

DISTR

For Action

(Attention:)

Internal
File: 3MII///

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LT COL LC FOSA
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Consent Form for Case Reports

Case Report: The Glucagonoma syndrome with Necrotising Migratory Erythema and Diarrhoea

Principal Investigator: **Rahm Makan, MBCHB (UKZN), Registrar**
University of Free State
Contact no: 072 144 6140

You are being asked to consider allowing Dr. Rahm Makan to use information about your condition to write what is called a case report. Case reports are typically used to share new unique information experienced by one patient during his/her clinical care that may be useful for other physicians and members of a health care team. A case report may be published in print and/or via internet dissemination for others to read, and/or presented at a conference. This form explains the purpose of this case report. Please read this form carefully and take your time to make your decision and ask any questions that you may have.

The purpose of this case report is to inform other physicians that the skin problem you experienced together with diarrhoea may be related to a tumour of the pancreas known as a Glucagonoma.

Your information being used for this case report includes clinical history, examination findings, blood test results, radiological investigations (annexure A) and photographs (annexure B).

Dr. Makan is obligated to protect your privacy and not disclose your personal information (information about you and your health that identifies you as an individual e.g. name, date of birth, medical record number). When the case report is published or presented, your identity will not be disclosed.

Although your personal information collected or obtained will be kept confidential and protected to the fullest extent of the law, there is a limited risk associated with this case report that could result in a loss of confidentiality by virtue of your unique experience.

You will not directly benefit from participating in this case report. The information that can be shared with other health care professionals, however, may improve the care that is received by others in the future.

Allowing your information to be used in this case report will not involve any additional costs to you. You will not receive any compensation.

Taking part in this case report is your choice (voluntary). You may choose not to take part or you may change your mind at any time. However, once the case report is written and published, it will not be possible for you to withdraw it. Your decision will not result in any penalty or loss of benefits to which you are entitled including the quality of care you receive.

You will be told about any new information relating to this case report that may affect you.

Your signature below means that you have read the above information about this Case Report and have had a chance to ask questions to help you understand how your information will be used and that you give permission to allow your information to be used in this case report.

If you have any questions please contact Dr. Makan at 072 144 6149.

SUBJECT CONSENT TO PARTICIPATE

Case Report:

The Glucagonoma syndrome with Necrotising Migratory Erethema and Diarrhoea

Name of Participant: Christa Janse Van Rensburg

By signing this form, I confirm that:

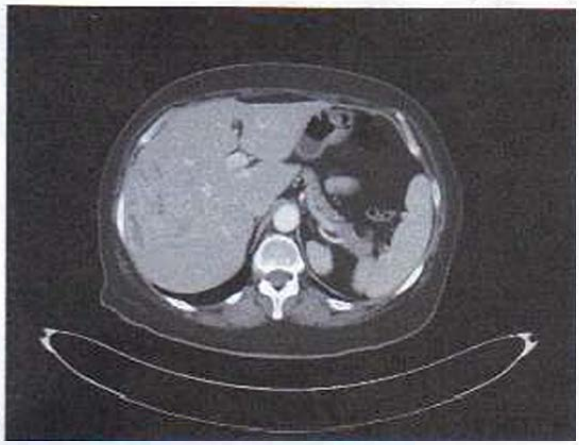
- The case report has been fully explained to me and all of my questions have been answered to my satisfaction
- I have been informed of the risks and benefits, if any, of allowing my information to be used in this case report
- I have been informed that I do not have to participate in this case report
- I have read each page of this form
- I authorize access to my personal health information (medical record), radiological investigations and photographs as explained in this form
- I have agreed to participate in this case report

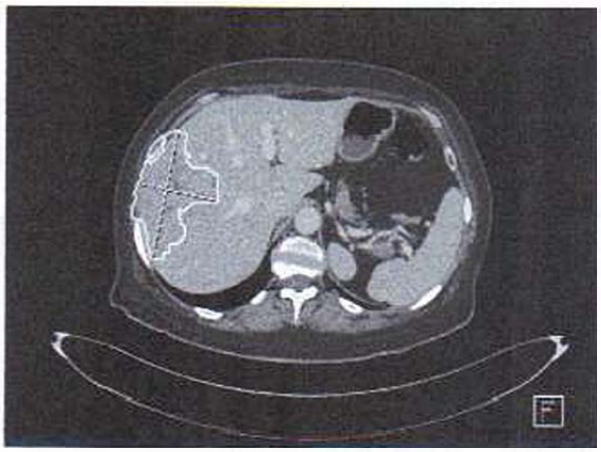
Christa Janse van Rensburg — Name of Participant

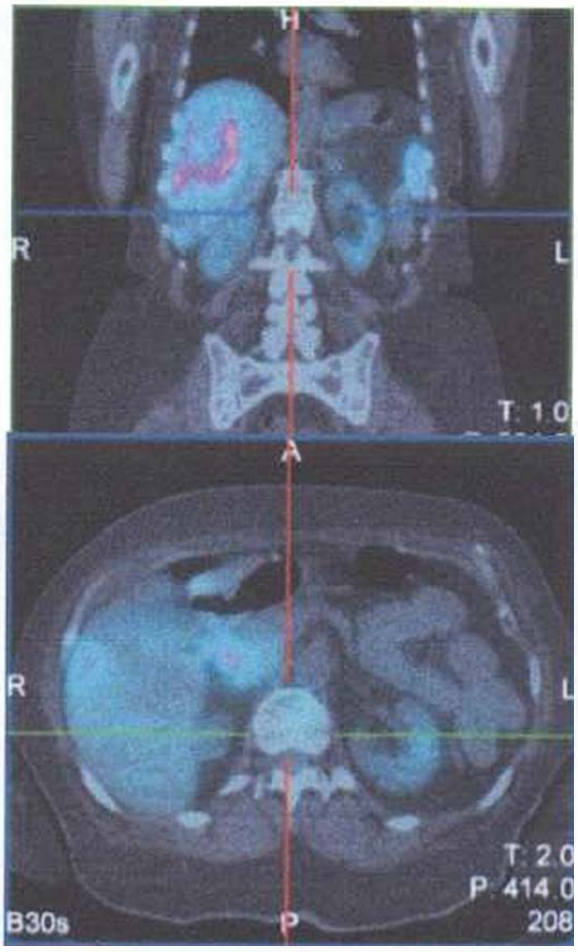
Signature

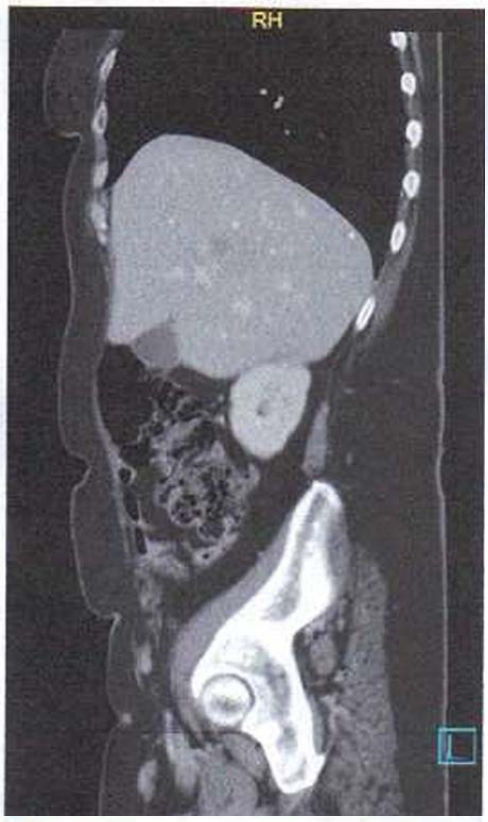
28-09-2017 — Date

Annexure A

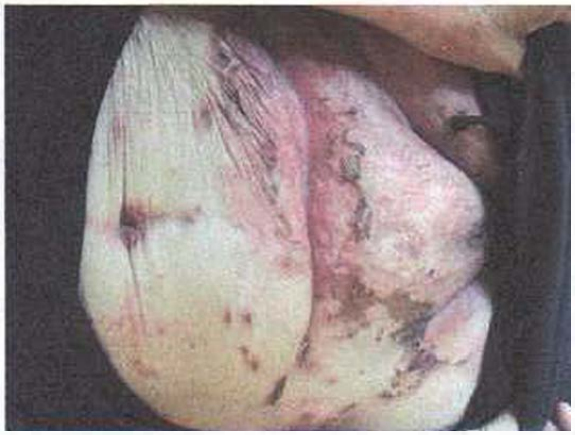


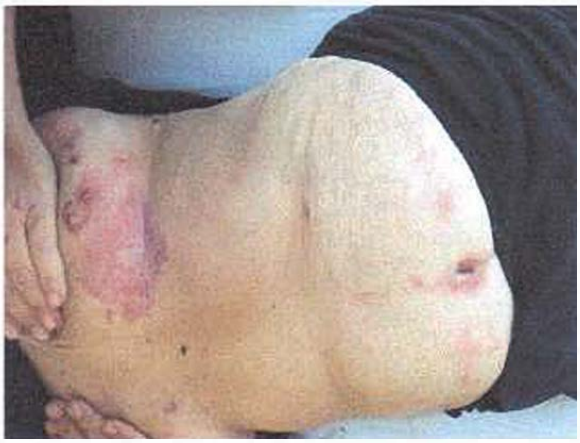


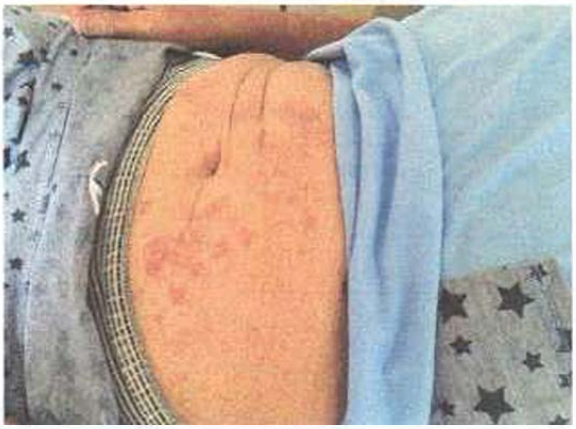


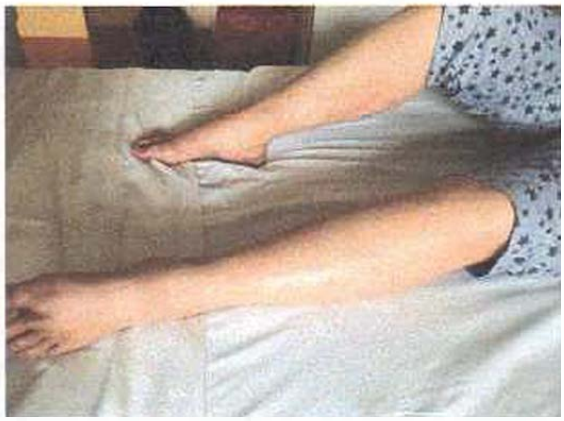


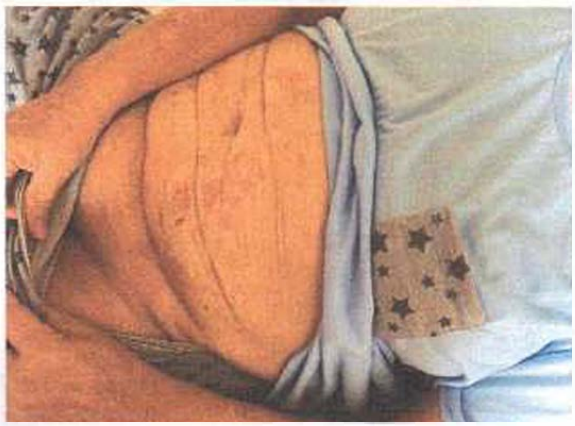
Annexure B

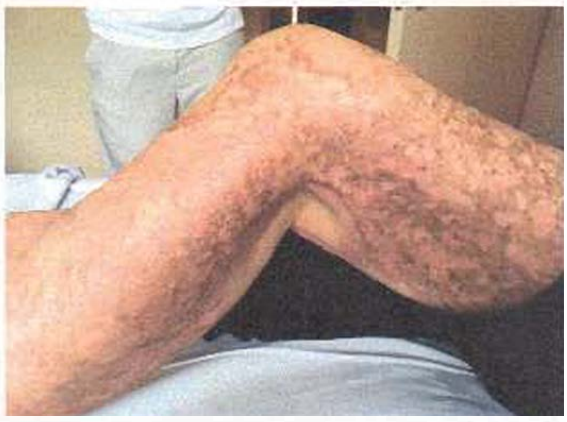












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UFS·UV HEALTH SCIENCES GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

02 October 2017

DR RAHM MAKAN
DEPT. OF INTERNAL MEDICINE
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr Rahm Makan

HSREC 86/2017 (UFS-HSD2017/0641)
PRINCIPAL INVESTIGATOR: DR RAHM MAKAN
SUPERVISOR: CLOETE VAN VUUREN
PROJECT TITLE: NECROTISING MIGRATORY ERETHEMA AND DIARRHOEA LEADING TO DIAGNOSIS OF NEUROENDOCRINE TUMOUR

APPROVED

1. You are hereby kindly informed that the Health Sciences Research Ethics Committee (HSREC) approved this protocol after all conditions were met. This decision will be ratified at the next meeting to be held on 31 October 2017.

2. The Committee must be informed of any serious adverse event and/or termination of the study.

3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.

4. A progress report should be submitted within one year of approval and annually for long term studies.

5. A final report should be submitted at the completion of the study.

6. Kindly use the **HSREC NR** as reference in correspondence to the HSREC Secretariat.

7. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

MS MGE MARAIS
HEAD: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE ADMINISTRATION

Updated By: **Rahm R Makan @ 10-May-2017 08:47:08 PM**

Application for Ethical Clearance

Guidelines to complete the Ethics Application

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Important:

1. All sections must be completed and all mandatory information must be included in the E-form otherwise you will not be able to submit.

2. The application must be brief, providing adequate information for expert review and also understandable to lay persons.

3. The application should be submitted before deadline dates.

*4. Remember to click on **'SAVE'** after each section and to click the **'COMPLETE'** box on the top right hand corner when all the fields are completed. **NEVER** click on **'SAVE' AFTER** the form has been **'COMPLETED'**.*

5. Please make sure that you also click the 'COMPLETE' box when all necessary documents are uploaded in the 'DOCUMENT CHECKLIST' and the Ethical Risk Assessment Checklist.

6. Click on 'SUBMIT' when all the information is complete and REMEMBER to ADD, (if applicable), your Supervisor/Study Leader/Promoter to the route.

*7. You have the option of viewing/ changing your application after being logged out. Just Log in: Click on **"MY ITEMS" next to My Profile***

8. Remember once you have 'submitted' then the application is in the route, and out of your possession.

Principal Investigator details

PI
Makan, Rahm R

Department	Internal Medicine (Bloemfontein Campus)
Employee/Student ID	UFS_2016395929
Email	rahm@live.co.za
Phone	0721446149

AFFILIATION

***Are you a B Tech student at the Central University of Technology?** No

***Are you a DTech/CUT Researcher** No

Please make sure that the PRINCIPAL INVESTIGATOR'S department is NOT displaying as "RESEARCH DEVELOPMENT" above

*** Does the PRINCIPAL INVESTIGATOR'S Associated Department (Department where your study is being done) and all other details above display correct (e.g. phone, email address etc.) ?** Yes ☑ No ☐

Researcher Status

*What is your Academic Status? Select from the list Post Graduate

Review Committee

***Select the applicable Ethics Review Committee/Submission type. (Click on the drop-down menu and select from list)** Health Sciences Case Reports/Series

HEALTH SCIENCES APPLICATION: CASE REPORT/SERIES

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YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

1: DETAILS OF APPLICANT/PRINCIPAL INVESTIGATOR

***PI Details:**
Makan, Rahm R

Full Name	Makan, Rahm R
Department	Internal Medicine (Bloemfontein Campus)
Phone	0721446149
Email	rahm@live.co.za

***Professional Registration:** ☑ Yes ☐ No **Registration #:** MP0765457

2: TITLE OF STUDY

***Title of case report/case series:**
Necrotising Migratory Erethema and Diarrhoea leading to diagnosis of Neuroendocrine Tumour

2.1: LAY SUMMARY

***Provide a lay summary of your protocol**
This is a case report on an exceptionally rare case of a Neuroendocrine tumour (Glucagonoma). The report will discuss this index case presentation as well as epidemiology, diagnostic modalities, pathophysiology of symptomos and manifestations as well as current treatment options including a literature review of current practice.

Note: Please use simple, clear language (Maximum Grade 8 reading level) and explain/ define all medical and technical terms. For guidance on the summary, please refer to the General Submission Guidelines

3: STUDY FOR DEGREE PURPOSES

***Is this study for degree purposes?** ☑ Yes ☐ No

***Name of Degree:** MMED
***Division:** FCP
Department: Internal Medicine
***Supervisor:** Cloete Van Vuuren
Contact No: 0832946684
***E-mail:** cloetevv@hotmail.com

4: COLLABORATING INVESTIGATORS

***Are there any other collaborating investigators participating in this research?** ☐ Yes ☑ No

5: WHERE WAS THE CASE STUDY OR CASE SERIES CONDUCTED?

***Select the location from the pick list:** Hospitals

***Use the text area below to indicate the location where you will be collecting data if the location was not listed in the pick list above and you had to choose 'Other'. If you chose a location from the pick list such as 'rural area' or 'hospital' then please use the text area to specify the location further e.g. exactly where/which rural area etc. Otherwise enter 'Not Applicable'.**
3 Military Hospital, Tempe, Bloemfontein

6: RATIONALE

***Please provide a rationale for the report/series.**
To increase awareness amongst the medical fraternity of this rare and easily misdiagnosed condition.

7: PROTECTING PATIENT CONFIDENTIALITY

***Please detail the steps taken to protect patient confidentiality**
Patients name and identity number, hospital number and date of birth will be confidential and excluded from case report.
Photographs will not expose patients face.
Blood results and radiographs will be used after the patients details are removed.

8: INFORMED CONSENT

***Was informed consent obtained from the patient(s)?** ☑ Yes ☐ No

9: STATEMENT OF CONFLICT OF INTEREST

The Principal Investigator is expected to declare any existing or potential conflict of interest that may affect the scientific integrity and ethical conduct of this research. For purposes of this section, 'immediate family' means the Principal Investigator's spouse or domestic partner and dependent children. **Please tick all that apply.**

9.1 No conflict of interest declared: ☑

I, nor any member of my immediate family, **do not** have any interest related to this research (e.g. financial interest) ☑

I, nor any member of my immediate family, **do not** have any relationships related to this research (e.g. board membership, consultative, executive, employment) or any entity with an ownership interest in the research other than the relationship of investigator. ☑

9.2 Conflict of interest declared: ☐

10. DECLARATIONS AND SIGNATURES

Note: This application will not be processed unless all the required declarations and signatures are completed.

Download the Investigator Declaration Template and print it out. Scan the document into the computer after signing it and upload it below.

Click on this link to download the template

10.1 Principal investigator

My signature confirms that:

i. Information in this application is true and accurate.

ii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.

iii. I will conduct the research according to all ethical, regulatory and legal requirements stipulated in the HSREC's Standard Operating Procedures.

iv. I will endeavour to publish and disseminate the findings of this case report/series.

10.2 Student Main Supervisor (if research is for a qualification) Applicable? ☑ Yes ☐ No

My signature confirms that:

i. The application is ready for submission for ethical clearance.

ii. Information in this application is true and accurate.

iii. The research has scholarly merit.

10.3 Co-supervisors Applicable? ☑ Yes ☐ No

My/our signature(s) confirm that:

i.Information in this application is true and accurate.

ii.I/we accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.

iii.I/we will conduct the research according to all ethical, regulatory and legal requirements as stipulated in the HSREC's Standard Operating Procedures.

10.4 Collaborating Investigators Applicable? ☐ Yes ☑ No

*** Upload the template after signing it by clicking on the icon to the right**

Appendix 1

EForm Name: ETHICS CLEARANCE APPLICATION
Page: HEALTH SCIENCES APPLICATION: CASE REPORT/SERIES
Section: 10. DECLARATIONS AND SIGNATURES
Question: Upload the template after signing it by clicking on the icon to the right.
File Name: Investigator declaration.PDF

HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

CASE REPORT/SERIES: INVESTIGATOR DECLARATION

The principal investigator, supervisor, as well as all sub- & co-investigators (where applicable) must sign this declaration.

1.1 INVESTIGATOR DETAILS AND ROLE IN THIS RESEARCH	
Title, Initials, Surname:	DR. R. MAKAN
Department/Institution:	INTERNAL MEDICINE
Phone:	072 144 6149
E-mail address:	rahm@live.co.za.

1.2 What is your role in this research? [✓]			
Principal investigator	☒	Co-investigator	☐
Sub-investigator	☐	Supervisor	☐
Other: Specify			☐

Title of Case Report/Series
Necrolising Migratory Erethema and diarrhoea leading to diagnosis of Neuroendocrine Tumour.

1. STATEMENT OF CONFLICT OF INTEREST

The Principal Investigator is expected to declare any existing or potential conflict of interest that may affect the scientific integrity and ethical conduct of this research. For purposes of this section, 'immediate family' means the Principal Investigator's spouse or domestic partner and dependent children. **Please tick ✓ all that apply.**

1.1 No conflict of interest declared:	
Neither I, nor any member of my immediate family, have any interest related to this research (e.g. financial interest)	☒
Neither I, nor any member of my immediate family, have any relationships related to this research (e.g. board membership, consultative, executive, employment) or any entity with an ownership interest in the research other than the relationship of-investigator.	☒

1.2 Conflict of interest declared:	☒ N/A
As Principal Investigator of this research I am aware of a potential conflict of interest. *Please describe and provide a plan to manage the conflict of interest in the space below:*	☐

2. DECLARATIONS AND SIGNATURES

2.1 Principal Investigator

My signature confirms that:

i. Information in this application is true and accurate.
ii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iii. I will conduct the research according to all ethical, regulatory and legal requirements stipulated in the HSREC's Standard Operating Procedures.
iv. I will endeavour to publish and disseminate the findings of this case report/series.

Signature of Principal Investigator		Date	09/05/2017
Print name	RAHMI MAKAN		

2.2 Student Main Supervisor (if research is for a qualification) ☐ N/A

My signature confirms that:

i. The application is ready for submission for ethical clearance.
ii. Information in this application is true and accurate.
iii. The research has scholarly merit.

Signature of Principal Investigator / Supervisor		Date	10 May 2017
Print name	JCJ VAN VUUREN		

Note: The main supervisor and student researcher are jointly responsible for the ethical conduct of this research from inception to dissemination of findings.

2.3 Co-supervisors ☐ N/A

My/our signature(s) confirm that:

i. Information in this application is true and accurate.
ii. I/we accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.
iii. I/we will conduct the research according to all ethical, regulatory and legal requirements as stipulated in the HSREC's Standard Operating Procedures.

Name	W.F. MOLENTZE	Signature		Date	10/5/2017.
Name		Signature		Date	
Name		Signature		Date	

2.4 Collaborating Investigators ☒ N/A

My/our signature(s) confirm that:

i. Information in this application is true and accurate.
ii. I accept full responsibility for the conduct of this research and the protection of participants' rights and welfare.

Updated By: **Rahm R Makan @ 09-Aug-2017 07:33:02 PM**

REQUESTED MODIFICATIONS / DOCUMENTS

Page 1

Indicate the changes made to this protocol

You have received a letter from the Ethics Committee containing provisions made by the reviewers. Please copy and paste all the provisions from the letter into the text area below OR upload the letter:
HSREC 86/2017 (UFS-HSD2017/0641) PRINCIPAL INVESTIGATOR: DR RAHM MAKAN SUPERVISOR: CLOETE VAN VUUREN PROJECT TITLE: NECROTISING MIGRATORY ERYTHEMA AND DIARRHOEA LEADING TO DIAGNOSIS OF NEUROENDOCRINE TUMOUR MODIFICATIONS REQUIRED 1. You are hereby kindly informed that, at the meeting held on 25 July 2017, the Health Sciences Research Ethics Committee (HSREC) reviewed the above research project. A decision could not be reached as there are modifications required to the protocol / outstanding requests from the HSREC. Please see below for details: 1.1. Documents: 1.1.1. Please upload a proper cover letter addressed to: The Chair, Health Sciences Research Ethics Committee, University of the Free State, wherein you clearly state your intention, namely to publish a case report and what the benefit of such a publication will be. 1.1.2. The consent form should include explicit consent to the use of imaging studies and photographs. She should be shown which photographs (of imaging studies, as well as of herself) are going to be published: it is best to include these photographs in the consent form. The patient should consent that these may be published in a medical journal. From the patient's name I deduct that she is Afrikaans-speaking: It is appropriate to give her an Afrikaans consent form. 1.1.3. You need permission from the institution where the patient was treated, namely from the office of the Chief: SA Military Health Services. 1.2. Ethical Risk Assessment: 1.2.1. You should tick that it is possible to identify the patient: she has an extremely rare condition with very specific skin changes and was treated in a small hospital. All the hospital nursing and medical staff will be able to recognize her from her photographs. This should be mentioned to her during consent taking

Upload the letter here:

* Were you required to change anything in the E-form? Yes ☑ No ☐

* Indicate the action that was taken in response to each remark
1.1.1. Cover letter amended appropriately. 1.1.2. Consent form amended and images included. The patient commented that she is comfortable with an English consent form. This was used. 1.1.3. Permission obtained from Chief of Clinical Services at 3 Military - Dr LC FOSA 1.2.1. Ammended

* Did any of the remarks pertain to documents that needed to be uploaded or changed? Yes ☑ No ☐

Required Documents (Click on the yellow + to add copies of documents)

* Add all the requested documents	* Please enter the name of the document:
	Cover Letter ammended
	Consent form ammended
	Authorisation from Military Hospital
	Ethical Risk Assessment Ammended

Appendix 1

EForm Name: MODIFICATIONS AND/OR REQUIRED DOCUMENTS
Page: Page 1
Section: Required Documents (Click on the yellow + to add copies of documents)
Question: Add all the requested documents
File Name: cover page.pdf

To:
The Chair, Health Sciences Research Ethics Committee,
University of the Free State

Requesting ethics clearance for intention to publish:

Case Report: Necrotising Migratory Erythema and Diarrhoea leading to Diagnosis of Neuroendocrine Tumour

Researchers: Principal Investigator: Rahm Makan

Supervisor: JCJ Van Vuuren

This benefit of this case report is the end result of publication which aims to increase awareness amongst medical professionals about a rare neuroendocrine tumour known as a Glucagonoma. It presents with a unique skin disease which can be easily misdiagnosed. This will be presented in the case report along with a relevant literature review of current treatment and diagnostic modalities as well as discussion of pathophysiology behind presenting symptoms.

Appendix 2

EForm Name: MODIFICATIONS AND/OR REQUIRED DOCUMENTS
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Consent Form for Case Reports

Case Report: The Glucagonoma syndrome with Necrotising Migratory Erythema and Diarrhoea

Principal Investigator: **Rahm Makan, MBCHB (UKZN), Registrar**
University of Free State
Contact no: 072 144 6149

You are being asked to consider allowing Dr. Rahm Makan to use information about your condition to write what is called a case report. Case reports are typically used to share new unique information experienced by one patient during his/her clinical care that may be useful for other physicians and members of a health care team. A case report may be published in print and/or via internet dissemination for others to read, and/or presented at a conference. This form explains the purpose of this case report. Please read this form carefully and take your time to make your decision and ask any questions that you may have.

The purpose of this case report is to inform other physicians that the skin problem you experienced together with diarrhoea may be related to a tumour of the pancreas known as a Glucagonoma.

Your information being used for this case report includes clinical history, examination findings, blood test results, radiological investigations (annexure A) and photographs (annexure B).

Dr. Makan is obligated to protect your privacy and not disclose your personal information (information about you and your health that identifies you as an individual e.g. name, date of birth, medical record number). When the case report is published or presented, your identity will not be disclosed.

Although your personal information collected or obtained will be kept confidential and protected to the fullest extent of the law, there is a limited risk associated with this case report that could result in a loss of confidentiality by virtue of your unique experience.

You will not directly benefit from participating in this case report. The information that can be shared with other health care professionals, however, may improve the care that is received by others in the future.

Allowing your information to be used in this case report will not involve any additional costs to you. You will not receive any compensation.

Taking part in this case report is your choice (voluntary). You may choose not to take part or you may change your mind at any time. However, once the case report is written and published, it will not be possible for you to withdraw it. Your decision will not result in any penalty or loss of benefits to which you are entitled including the quality of care you receive.

You will be told about any new information relating to this case report that may affect you.

Your signature below means that you have read the above information about this Case Report and have had a chance to ask questions to help you understand how your information will be used and that you give permission to allow your information to be used in this case report.

If you have any questions please contact Dr. Makan at 072 144 6149.

SUBJECT CONSENT TO PARTICIPATE

Case Report:

The Glucagonoma syndrome with Necrotising Migratory Erethema and Diarrhoea

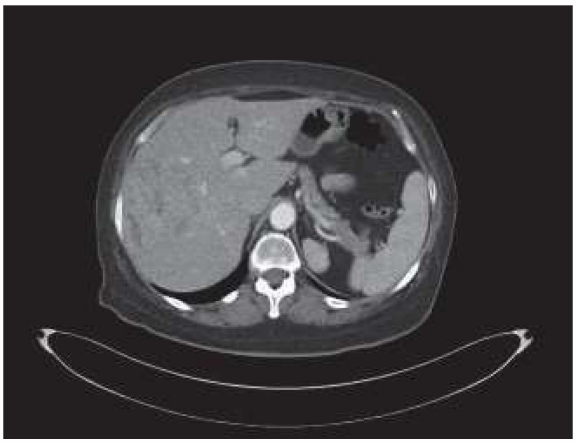
Name of Participant: Christa Janse Van Rensburg

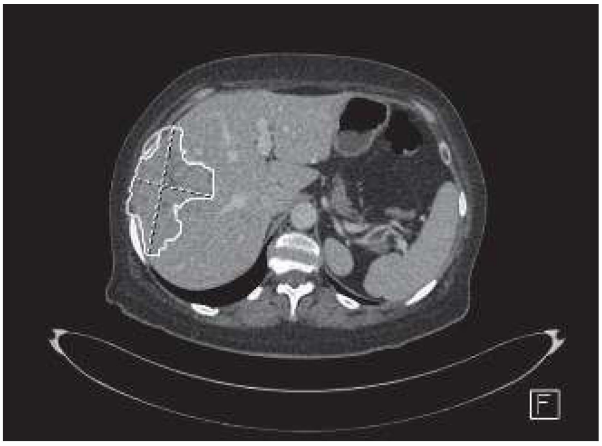
By signing this form, I confirm that:

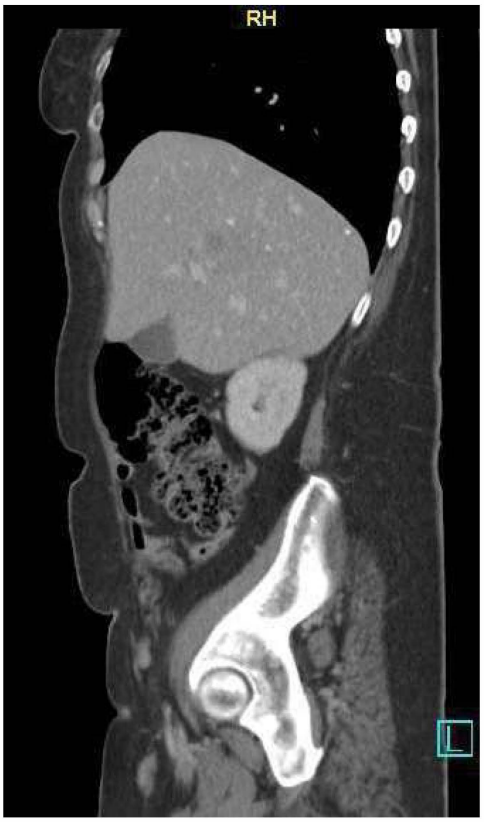
- The case report has been fully explained to me and all of my questions have been answered to my satisfaction
- I have been informed of the risks and benefits, if any, of allowing my information to be used in this case report
- I have been informed that I do not have to participate in this case report
- I have read each page of this form
- I authorize access to my personal health information (medical record), radiological investigations and photographs as explained in this form
- I have agreed to participate in this case report

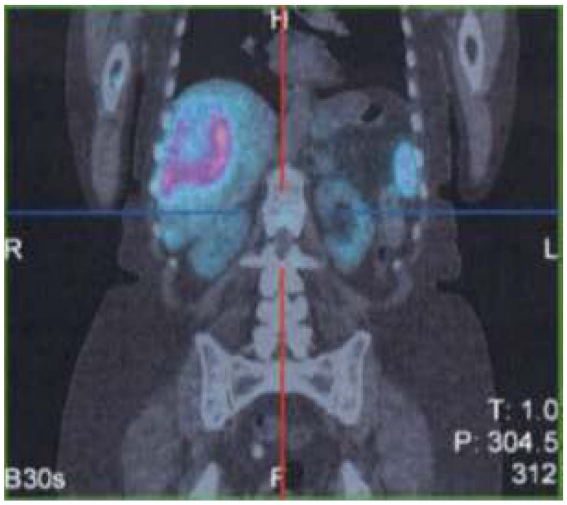
Name of Participant	Signature	Date

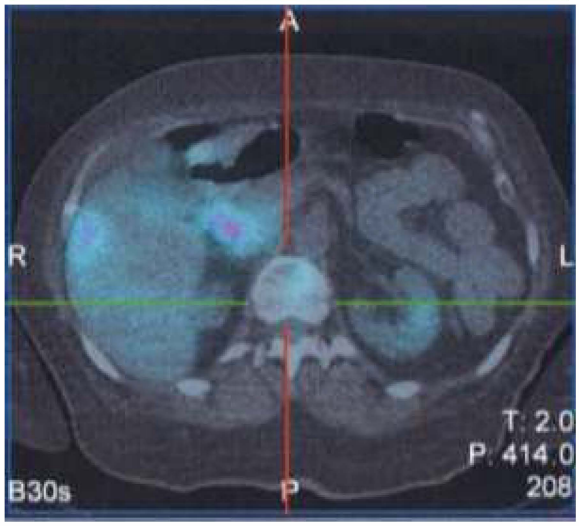
Annexure A



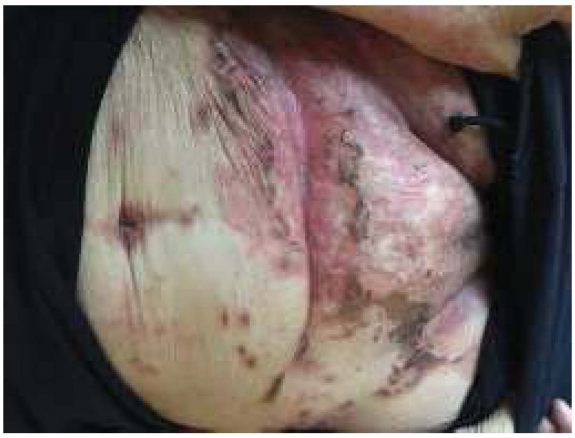


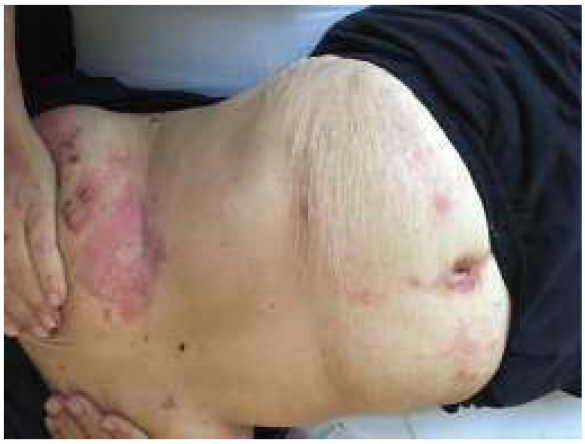


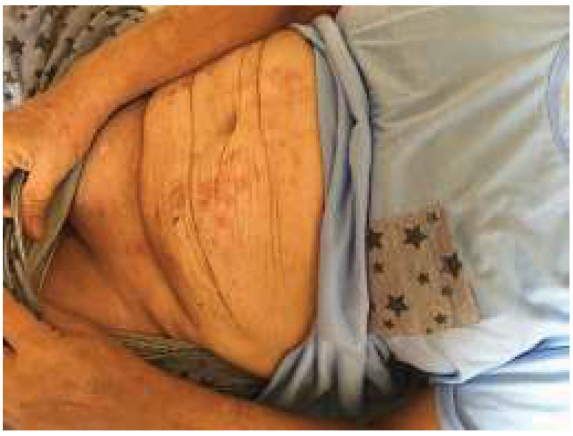


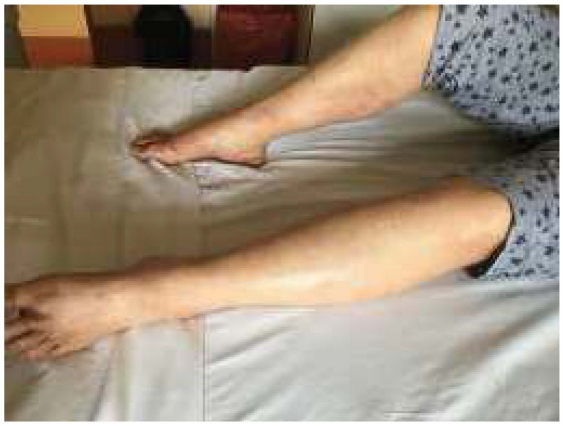


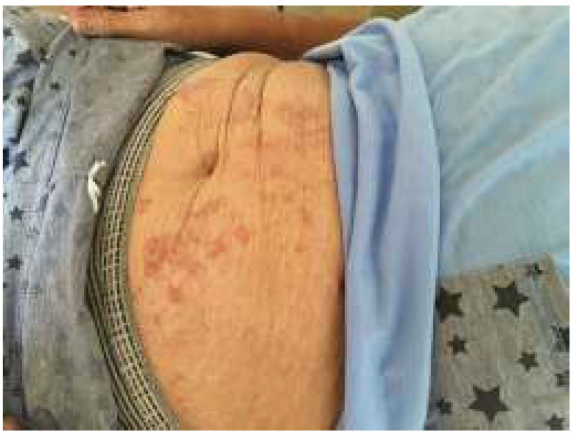
Annexure B

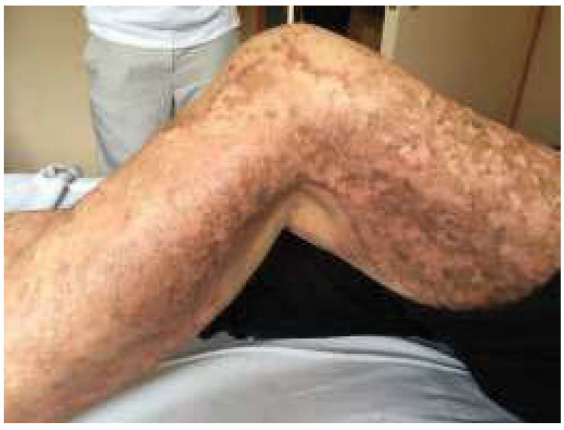












Appendix 3

EForm Name: MODIFICATIONS AND/OR REQUIRED DOCUMENTS
Page: Page 1
Section: Required Documents (Click on the yellow + to add copies of documents)
Question: Add all the requested documents
File Name: 3mil auth.PDF

Dr Rahm Makan
Internal Medicine
University of Free State

To Dr LC Fosa
Head of Clinical Services
3 Military Hospital

Re: Request for permission of use of patient information

I am a medical registrar in Internal Medicine. During my rotation at 3 Military Hospital, I encountered a case that is suitable for my MMED dissertation as well as publication in a medical journal.

The patients details are: Mrs Christa Janse Van Rensburg
IMS no 77542330
Date of Birth 12/10/2017
Diagnosis: Metastatic Glucagonoma

I received written permission from the patient to use her information and images.

Will you please grant permission to use information from 3 Military Hospital to enable me to get ethics clearance.

Yours Sincerely

Rahm Makan

Cell: 072 144 6149
Email: rahm@live.co.za

APPROVED
LT COL LC. FOSA
8300388PE

3MH/C//

Telephone: (051) 402 2375
Facsimile: (051) 402 2375
Enquiries: Lt Col JCJ van Vuuren

3 Military Hospital
Private Bag X40003
Brandhof
9324

2 August 2017

Lt Col LC Fosa

Re: Permission to use information from an individual patient

Please see the attached request from dr Makan. The patient agreed to her information being used. We need your permission to get this past the ethics committee.

Yours sincerely

(J.C.J VAN VUUREN)
PRINCIPAL SPECIALIST: INTERNAL MEDICINE: 3 MILITARY HOSPITAL: LT COL

DISTR

For Action
(Attention:)

Internal
File: 3MH//

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LT COL LC. FOSA
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Appendix 4

EForm Name: MODIFICATIONS AND/OR REQUIRED DOCUMENTS
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Section: Required Documents (Click on the yellow + to add copies of documents)
Question: Add all the requested documents
File Name: ethical risk assessment ammeded.pdf

Updated By: **Rahm R Makan @ 06-Aug-2017 09:25:57 PM**

ETHICAL RISK ASSESSMENT CHECKLIST

Please Complete Each Section to Indicate your Risk Level

NOTE: You will not be able to complete the checklist if you have not answered all the questions!

1. PARTICIPANTS

Yes *1.1 It is possible that an individual or definable group will be identified during research process and it is likely to be of concern.

No *1.2 The participation of children and young people (under 18 years of age) other than in normal instructional or educational activities.

No *1.3 Participants may include children or young people (under 18 years of age) without parent consent.

No *1.4 Participants may include those who are unable to give informed consent and consent will only be obtained at a later stage.

No *1.5. Participants may include those who are in a dependent relationship (such as student/ lecturers, patients/ doctors, employees/ employers).

No *1.6 Recruitment of participants from vulnerable groups such as previously disadvantaged persons, people living in poverty, pregnant women, the elderly, the mentally ill or handicapped, prisoners, etc.

2. DATA COLLECTION

No *2.1 Collection, use or disclosure of personal information from an organisation without consent of the participant.

No *2.2 Collection, use or disclosure of personal information from a private sector organisation without consent of the participant.

Yes *2.3 Audio-visual recording of participants which may be of a sensitive or compromising nature.

No *2.4 Use of a questionnaire, survey or interview (where the identity of the participant may or may not be recorded) that might be expected to cause discomfort, embarrassment, or psychological stress or harm.

No *2.5 The usage of potentially identifiable (including coded) storage methods

3. PROCEDURES

No *3.1 Administration of drugs, placebo or any other forms of medical treatment (including ionising radiation) to participants.

No *3.2 Any form or physically invasive diagnostic, therapeutic or medical procedure such as blood collection, body fluid or tissue samples, exercise regime or physical examination.

No *3.3 Physical pain (i.e. more than mild discomfort) or psychological stress is likely to result from participation.

No *3.4 Research involving the deception of participants, concealment or covert observation.

No *3.5 Participants will be offered payments or inducements to encourage their involvement in the project.

No *3.6 Disclosure of the results of the project could put participants at the risk of criminal or civil liability or be damaging to their financial standing, employability, professional or personal relationships.

4. RESEARCHER

No *4.1 There is a possible risk of physical threat, abuse or psychological trauma as a result of actual or threatened violence or the nature of what is disclosed during the interaction.

No *4.2 There is a possible risk of being in a comprising situation, in which there might be accusations of improper behaviour.

No *4.3 There is an increased exposure to risks of everyday life and social interactions, such as road accidents and infectious illness.

5. ADDITIONAL INFORMATION/ MOTIVATION

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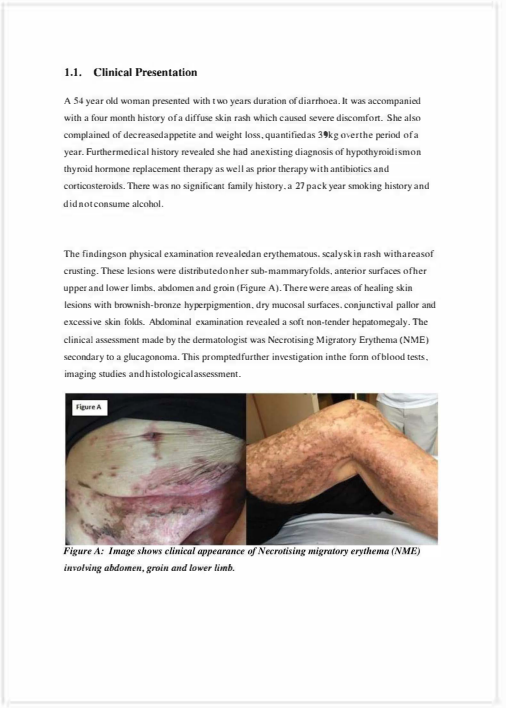

1.1. Clinical Presentation

A 54 year old woman presented with two years duration of diarrhoea. It was accompanied with a four month history of a diffuse skin rash which caused severe discomfort. She also complained of decreased appetite and weight loss, quantified as 3kg over the period of a year. Further medical history revealed she had an existing diagnosis of hypothyroidism on thyroid hormone replacement therapy as well as prior therapy with antibiotics and corticosteroids. There was no significant family history, a 27 pack year smoking history and did not consume alcohol.

The findings on physical examination revealed an erythematous, scaly skin rash with areas of crusting. These lesions were distributed on her sub-mammary folds, anterior surfaces of her upper and lower limbs, abdomen and groin (Figure A). There were areas of healing skin lesions with brownish-bronze hyperpigmention, dry mucosal surfaces, conjunctival pallor and excessive skin folds. Abdominal examination revealed a soft non-tender hepatomegaly. The clinical assessment made by the dermatologist was Necrotising Migratory Erythema (NME) secondary to a glucagonoma. This prompted further investigation in the form of blood tests, imaging studies and histological assessment.

Figure A

Figure A: Image shows clinical appearance of Necrotising migratory erythema (NME) involving abdomen, groin and lower limb.

MMED Necrotising migratory erythema leading to the diagnosis of a metastatic glucagonoma without diabetes

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- ✔ The text is single-spaced; uses a 12-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
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Abbreviations

These should be spelt out when first used in the text and thereafter used consistently. Scientific measurements: These should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl. If in doubt, refer to 'uniform requirements' above. Illustrations: Figures consist of all material that cannot be set in type, such as photographs and line drawings. If any tables or illustrations submitted have been published elsewhere, the author should obtain written consent to republication from the copyright holder and the author(s). All illustrations, figures etc must be of high resolution/quality, preferably jpeg or equivalent but not PowerPoint, and must be uploaded as separate

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References

References should be inserted in the text as superior numbers and should be listed at the end of the article in numerical and not in alphabetical order. Authors are responsible for verification of references from the original sources. References should be set out in the Vancouver style using approved abbreviations of journal titles; consult the List of Journals in Index Medicus for these details.

Unpublished observations and personal communications may be cited in the text, but not in the reference list. Sample references can be found at: http://www.nlm.nih.gov/bsd/uniform_requirements.html

Articles in Journals

- *Standard journal article*
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- *More than six authors:*
  Rose ME, Huerbin MB, Melick J, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Books

- *Personal author(s)*
  Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Electronic Material

- *Journal article on the Internet*
  Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 3 p.]. Available from: http://www.nursingworld.org/ AJN/2002/june/Wawatch.htm. Accessed 3 June 2007
- *Monograph on the Internet*
  Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/. Accessed 6 January 2007
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9. All photographs must be at 300 dpi and clearly marked according to the figure numbers in the text. (Figure 1, Table II, etc.)
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11. All numbers below ten, without percentages or units, must be written in words.
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Necrotising migratory erythema leading to the diagnosis of a metastatic glucagonoma without diabetes

Rahm Makan & Cloete Van Vuuren

To cite this article: Rahm Makan & Cloete Van Vuuren (2020): Necrotising migratory erythema leading to the diagnosis of a metastatic glucagonoma without diabetes, Journal of Endocrinology, Metabolism and Diabetes of South Africa, DOI: 10.1080/16089677.2020.1793487

To link to this article: https://doi.org/10.1080/16089677.2020.1793487

Published online: 05 Aug 2020.

Journal of Endocrinology, Metabolism and Diabetes of South Africa 2020: 1–2
https://doi.org/10.1080/16089677.2020.1793487

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

CASE REPORT

Necrotising migratory erythema leading to the diagnosis of a metastatic glucagonoma without diabetes

Rahm Makan* **and Cloete Van Vuuren**

Department of Health Sciences, University of the Free State, Bloemfontein, South Africa
**Correspondence: rahm@live.co.za*

A case of necrotising migratory erythema (NME), which is one of the distinctive paraneoplastic skin manifestations associated with the glucagonoma syndrome, is described and discussed. In 80% of all patients with glucagonoma, NME is the first clinical sign. The glucagonoma syndrome is a constellation of clinical features: NME, weight loss, anaemia, diabetes, diarrhoea, thromboembolism and neuropsychiatric symptoms. The global incidence of glucagonoma is one in 20 million people per year. The male to female ratio is 0.8:1 with the mean age of diagnosis being 52.2 years. The median time in relation to the initial onset of symptoms and the correct diagnosis is 3.5 years. The 10-year survival rate in patients with metastatic disease is 51.6% and without metastatic disease 64.3%. SPECT scan has a sensitivity range of 67–100% for detecting neuroendocrine tumours. Differential diagnoses of other skin conditions that mimic NME are: bullous pemphigoid, vasculitis, acrodermatitis enteropathica, chronic mucocutaneous candidiasis, seborrhoeic dermatitis, contact dermatitis, pellagra, inflammatory bowel disease, liver cirrhosis, coeliac disease, chemical burns, eczema, herpes etc. A satisfactory response to somatostatin as medical therapy in a case-study patient with metastatic disease is reported.

Keywords: dermatitis, diarrhoea, glucagon, groin, neuroendocrine, octreotide, pancreas, pulmonary embolus, rash, skin, somatostatin, SPECT, venous thromboembolism, zinc

A 54-year-old woman presented with a four-month history of a diffuse skin rash, which did not respond to oral corticosteroids prescribed by a dermatologist. She also complained of diarrhoea, loss of appetite and weight loss of 39 kg over a year. She had a 27 pack/year smoking history, and was on thyroid hormone replacement therapy. There was no significant family history of any medical conditions.

She had an erythematous, scaly skin rash with areas of crusting, distributed on her sub-mammary folds, anterior surfaces of her upper and lower limbs, abdomen and groin with areas of healing skin lesions characterised by brownish-bronze hyperpigmentation (Figure 1). Her mucosal surfaces were dry and she had conjunctival pallor. She had normal blood glucose but was anaemic with a haemoglobin of 10.7 g/dl.

On abdominal computerised tomography (CT) scan there was a large heterogeneous mass in the liver and multiple sclerotic lesions in vertebrae, pelvis and proximal femurs in keeping with metastatic foci. Single photon emission computerised tomography (SPECT) with Octreoscan™ (octreotide uptake scan) had focal increased areas of uptake in the head of the pancreas consistent with a glucagonoma and increased uptake in the liver, as well as skeletal metastases. The immunohistochemical stains on liver biopsy showed metastatic neuroendocrine tumour cells. Confirmation using a monoclonal antibody stain specifically for glucagon confirmed a glucagonoma. Serum glucagon levels were unavailable at the laboratory.

Our diagnosis was a metastatic glucagonoma presenting with necrotising migratory erythema (NME).

NME is a cutaneous, paraneoplastic manifestation due to long-standing high glucagon levels[1] causing diarrhoea as well as malabsorption with deficiency of zinc and other essential fatty acids and minerals.[2,3] Excess glucagon leads to increased arachidonic acid formation in the skin.[1] Friction in the intertriginous areas causes activation of the inflammatory cascade.[1] A differential diagnosis includes: bullous pemphigoid, vasculitis, acrodermatitis enteropathica, chronic mucocutaneous candidiasis, seborrhoeic dermatitis, contact dermatitis, pellagra, inflammatory bowel disease, liver cirrhosis, coeliac disease, chemical burns, eczema, herpes, etc.[4]

The global incidence of glucagonoma is one in 20 million people per year.[5] A functional glucagonoma presents with a glucagonoma syndrome: NME, weight loss, anaemia and diabetes;[6] however, all features may not be present concomitantly. Additional clinical features may include diarrhoea, thromboembolism and neuropsychiatric symptoms.

Our patient was treated with zinc (50 mg eight hourly per os) and dietary protein supplementation (Fresubin®) on which the skin improved. She was then started on intramuscular octreotide injections (Sandostatin® LAR 20 mg IMI monthly).

At the initial follow-up, random glucose was still normal; the skin rash and diarrhoea had resolved. Follow-up SPECT was done at 12 months (no progression), 18 months (no progression) and two years (evidence of progression). Eighteen months after diagnosis the patient presented with a pulmonary embolus, confirmed by CT pulmonary angiogram.

With this case presentation, we wish to highlight NME as a paraneoplastic phenomenon of a functional glucagonoma that presented without diabetes. Prophylactic anticoagulation should be considered once the diagnosis of glucagonoma has been confirmed, due to the increased risk and the high mortality

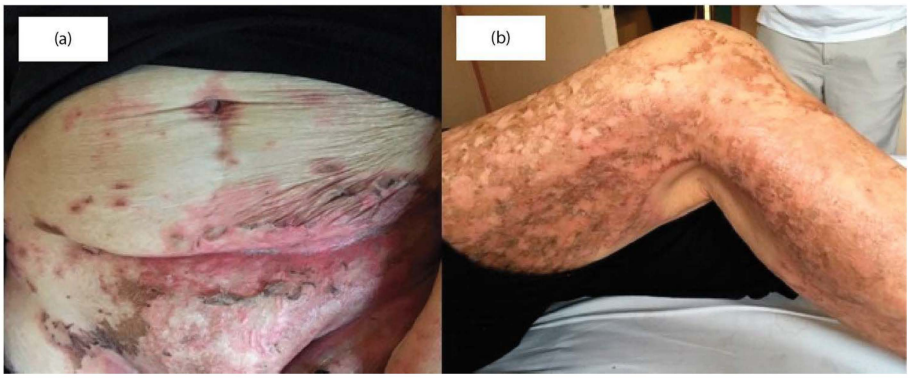

Figure 1. Image on the left shows clinical appearance of necrotising migratory erythema (NME) involving abdomen and groin, image on the right shows NME involving the lower limb.

associated with pulmonary embolism. Although patients diagnosed before the onset of metastatic disease may be cured surgically, medical therapy can still offer a good quality of life in the event of metastatic disease, as demonstrated in this case.

Disclosure statement – No potential conflict of interest was reported by the author(s).

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Received: 22-04-2020 Accepted: 6-07-2020