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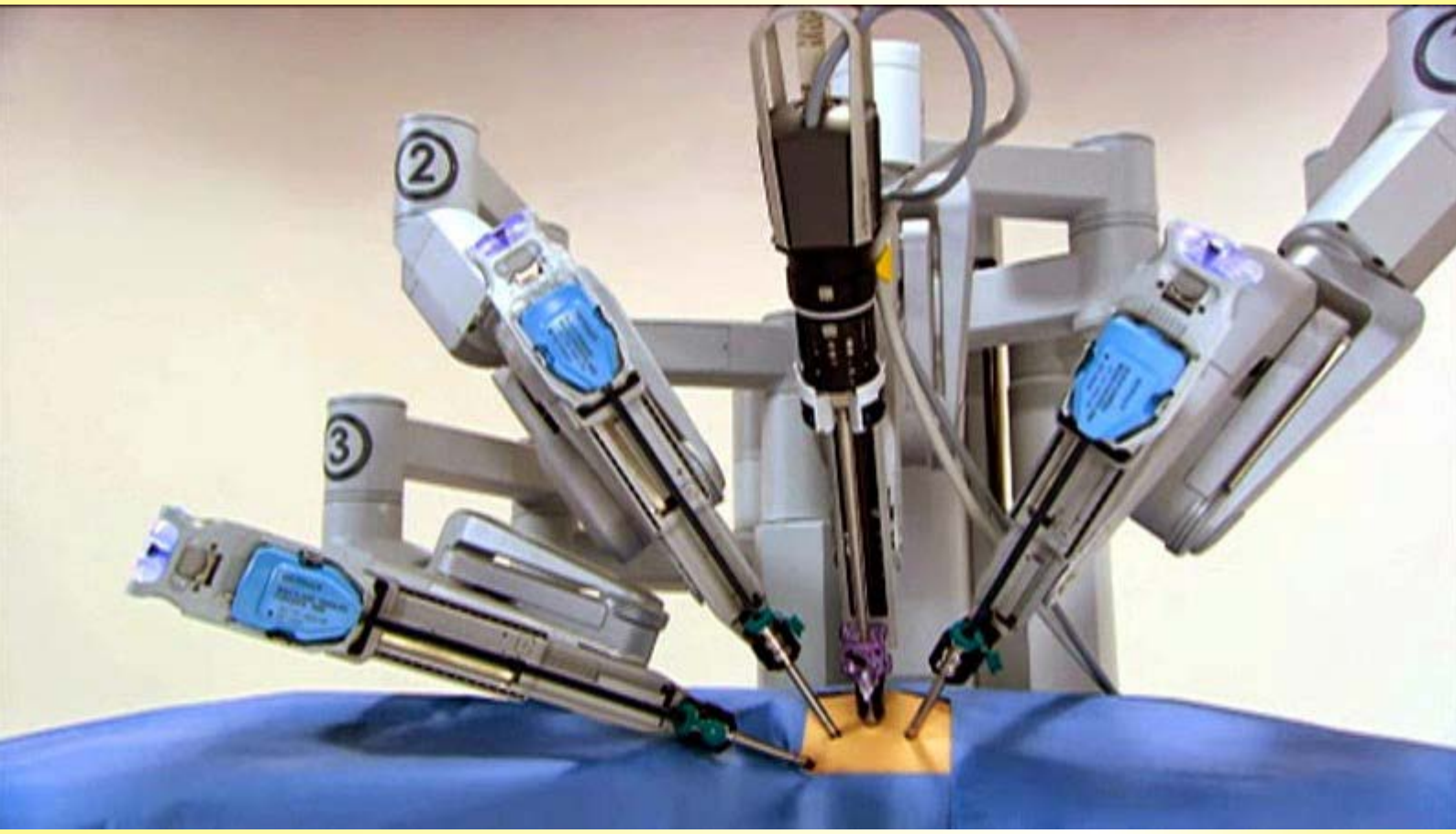

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Review

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Cellular and Molecular Cascades during Liver Regeneration

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ABSTRACT

The demand for organs such as the liver for patients with end stage disease is greater than what is currently available. Thus, there is a dire need to have alternative solutions, for which none exist at the moment. Investigating the key underlying mechanisms involved not only in liver regeneration and repair, but also in development, can give us a better understanding of how to promote a pro-regenerative phenotype in the liver. This review will focus on the cellular and molecular aspects of liver regeneration and address signaling mechanisms involved in liver development and how they are recapitulated in regeneration after a partial hepatectomy.

KEYWORDS: Liver; Regeneration; Hepatectomy; Stem cell; Healing; Inflammation.

ABBREVIATIONS: PHx: Partialhepatectomy; HSC: Hepatic Stellate Cells; BECs: Biliary Epithelial Cells; STM: Septum Transversum Mesenchyme; IL-6: Interleukin-6; FSCs: Facultative Stem Cells; Ang2: Angiopoietin 2; GFAP: Glial Fibrillary Acidic Protein; GFP: Green Fluorescent Protein; Hh: Hedgehog.

PREFACE

The liver's remarkable regenerative capacity was first described by the Greeks in the legend of Prometheus, a Titan who was banished by Zeus to eternal punishment. He was chained to a rock on a mountain, where an eagle would eat his liver daily, only to have it regenerate every night. To this date, we still do not have a clear idea how the liver recovers following injury.

INTRODUCTION

The liver is known for its imperative roles in metabolic homeostasis, immune regulation, bile secretion, serum protein synthesis and detoxification properties. The majority of blood flow that enters the liver is from the spleen, pancreas and intestines via the portal vein. This blood gets filtered from toxins and drugs before entering the heart to be circulated to the rest of the body. Thus, the liver is subjected to routine exposure to damaging agents. It has been hypothesized that the liver has evolved to become a highly regenerative organ to counter these toxins,[1] because liver dysfunction and failure can ultimately lead to death. It is yet to be demonstrated whether the liver's remarkable regenerative capacity is due to several cell types or a single cell of origin.

One of the most studied models of cell organ and tissue regeneration is liver regeneration after a 2/3 Partialhepatectomy (PHx). Different methods of liver resection are used to obtain the desired amount of liver mass loss. When performing a PHx, the vessels and ducts at the pedicel of the particular lobe must be ligated prior to cutting the lobe. Typically, the left lateral

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lobe and median lobes are removed, which equates to 67% of the liver mass.[2] There is an impressive increase in hepatocyte proliferation, which peaks at 36 hours,[2] followed by reconstitution of non-parenchymal cells after surgical liver resection as seen in animals. This surgical model has become popular over the last few years and gained acceptance by the majority of the research community for numerous reasons. The first reason being due to the multi-lobe structure of the liver, resection of different segments can be done without disturbing the remnant lobe(s). Thus, regeneration of the remaining lobes is accomplished through liver specific mechanisms and not due to acute inflammation or necrosis,[3,4] which is observed during liver laceration. Second, the procedure can be done in 10-15 minutes and regeneration is triggered almost instantly, which can be tracked temporally through different phases. Third, the procedure is easily reproducible and if done correctly, all animals will survive.[2]

Due to the absence of any significant inflammation or injury to the remaining lobes after a PHx,[4] there is no reported observation of stem cell activation or cellular reprogramming. In fact, after a PHx, the liver does not regrow the resected lobes but the remaining lobes, compensate for the loss via proliferation and increase in hepatocyte size. This process is referred to as "compensatory hypertrophy"[5,6] but we will continue to use "liver regeneration" as it is still a widely used term in this field. Previous studies have shown that during liver regeneration, almost all the hepatocytes undergo1-2 rounds of replication to restore normal liver mass.[6,7] However, more recent findings using modern lineage tracing and imaging techniques demonstrate that cellular hypertrophy is a significant contributor to the compensatory response and that hepatocytes undergo on average only 0.7 rounds of cell division in mice. The first 4 hours after a PHx is known as the "priming phase" as hepatocytes prepare to respond to various cytokines by substantially changing their gene expression, including up-regulation of anti-proliferative genes.[8] It is speculated that it is during this phase that hepatocyte hypertrophy is initiated.

Considering that healing involves several stages starting with inflammation, it is not clear whether the regenerative capacity of liver is mainly due to the absence of significant inflammation or the internal capacity of liver by itself to deliver the regeneration capacity. Part of this might be due to its unique histology and anatomical position, which we will discuss here.

LIVER ANATOMY

The liver is made of liver lobules, which are hexagonal in shape with a portal triad in each corner and a central vein in the center[9] (Figure 1A). The portal triad consists of a bile duct, portal venule and portal arteriole. Hepatocytes work to absorb metabolites and toxins, which have entered the liver through the portal vein. Bile is secreted from hepatocytes into the bile ducts, which will eventually enter the gall bladder for storage and released into the duodenum. Sinusoids are lined with endothelial cells forming the blood vessels. They drain the blood from the portal venules and arterioles into the central vein to be taken back to the heart. Inside the sinusoids are Kupffer cells, which are the resident macrophages of the liver. These cells work to cleanse the blood before it enters the central vein. Hepatic Stellate Cells (HSC) are located in the area between the sinusoids and hepatocytes, known as the space of Dissé[10] (Figure1B).

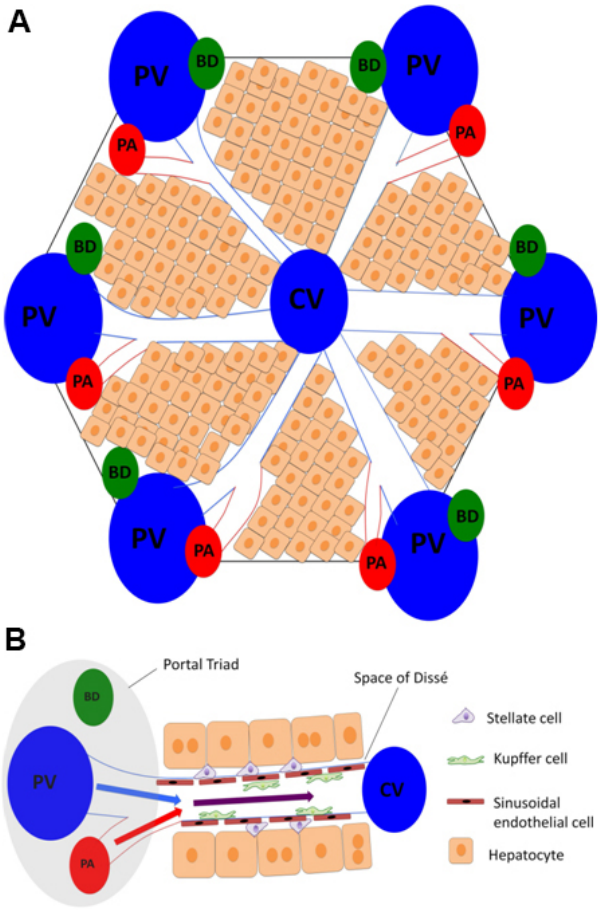

Figure 1: The functional unit of the liver. (A) The liver lobule. (B) The cell populations between the portal triad and central vein.

OVERVIEW OF LIVER DEVELOPMENT

Hepatocytes make up approximately 70% of the mass of the adult organ and are derived from embryonic endoderm, as are Biliary Epithelial Cells (BECs), also known as cholangiocytes. Other cells populating the liver include stellate cells, Kupffer cells and endothelial cells, which are of mesodermal origin. Through developmental studies on various animal models such as mouse, chicken, zebrafish, and Xenopus, many genes and molecular pathways have been identified that regulate embryonic development. These studies have enabled scientists to identify pathways implicated in liver regeneration in adult animals and humans. The regenerative mechanisms appear to recapitulate what is observed during development.

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The endoderm germ layer develops during gastrulation and forms a primitive gut tube that is subdivided into foregut, mid-gut, and hindgut regions. Fate mapping studies have demonstrated that the embryonic liver originates from the ventral foregut endoderm at embryonic day 8.0 of gestation (e8.0).[11] The thickening of the ventral foregut epithelium at e9.0 results in a hepatic diverticulum, which is the first indicator of liver development. The anterior segment of the hepatic diverticulum gives rise to the liver and intrahepatic biliary tree, while the posterior segment forms the gallbladder and extra-hepatic bile ducts. Preceding vascularization of the liver bud, at e9.0 endothelial precursor cells are situated between the epithelial cells and the Septum Transversum Mesenchyme (STM). Expression of vascular endothelial growth factor receptor 2 (Vegfr-2) has been shown to be essential as embryos that lack this gene fail to produce endothelial cells and hepatoblasts cannot go on to occupy the STM.[12]

During e9.5, the liver bud forms through the hepatic endoderm cells, known as hepatoblasts, and occupying the STM.[13,14] The STM provides the hepatic fibroblasts and stellate cells.[15] Starting at e10 until e15, liver bud gets invaded by hematopoietic cells as its development accelerates in order to become the main hematopoietic organ of the fetus. Thus, liver development involves contributions from tissues of endoderm and mesoderm origin. Hepatoblasts have bi-potential properties. Hepatoblasts that surround the portal vein differentiate to cholangiocytes, which form the primitive bile ducts also known as ductal plates. Primitive cholangiocytes express markers: Sry box containing gene 9 (Sox9), Ostepontin (OPN), and EpCAM. The remaining hepatoblasts in the parenchyma differentiate into hepatocytes.[16]

ESSENTIAL FACTORS DURING LIVER DEVELOPMENT

The regional identity of the endoderm seems to be contingent upon the spatial gradients of FGF, Wnt, BMP and retinoic acid secreted from the adjacent mesoderm.[17] However, it is still not understood how these pathways specify regional identity. Studies on chick and Xenopus suggest that FGF and Wnts released from the posterior mesoderm suppress foregut fate and promote hindgut development.[18] To establish foregut identity Wnt and FGF4 signaling needs to be inhibited in the anterior mesoderm. Inhibiting β-catenin, a downstream effector molecule in Wnt signaling, results in activation of Hhex, leading to ectopic liver buds in the intestine.[17] Interestingly, by e10, β-catenin has the opposite effect and promotes hepatic growth.[19] The specific Wnt ligands that effect hepatogenesis are still unknown. Experiments on chick embryos show that Wnt9a expressed in the sinusoidal wall is essential for liver bud growth through proliferation of hepatoblast and hepatocytes in culture.[12] In zebrafish, Wnt2b expression in the lateral plate mesoderm has been shown to be necessary for liver development. Wnt2 is also expressed in the lateral plate mesoderm and cooperates with Wnt2bbto control liver specification and proliferation in zebrafish.[20] The combined role of these signaling molecules is essential for liver specification because blocking them causes liver agenesis.[21]

In terms of hepatoblast proliferation and differentiation, hedgehog signaling is involved in promoting the proliferative response and subsequently needs to be shut off for differentiation to occur in a timely manner.[22]

Jagged-1, a Notch ligand is known to be expressed in the portal mesenchyme, which activates Notch-2 in neighbouring hepatoblasts, to promote differentiation of hepatoblasts into bile ducts.[23] Loss of Jag1 expression in the portal vein mesenchyme causes duct development to stall midway during ductal plate morphogenesis, leading to a paucity of bile ducts.[24]

Despite advancements in system biology and cell lineage studies, the cellular and molecular mechanisms of liver regeneration are still not clear. The information we learn and gather from regeneration of the liver may be used and applied to enhance regeneration of other organs. Here, we summarize the molecular and cellular mechanisms of liver regeneration after a PHx.

THE CELLULAR RESPONSE AFTER A PHx

Proliferation is the main method of liver regeneration after a PHx.[25] In mice it takes one week for the liver to return to 75% of its original size. The regenerative response involves constitution of hepatocytes first followed by biliary epithelial cells and then non-parenchymal cells.[26] Although cellular proliferation is the key regenerative mechanism, cellular hypertrophy is also observed.[6] Impaired hepatocyte proliferation is observed in aged mice, which is reversed in pregnant mice. Pregnant mice recover from a PHx at rates comparable to younger mice through hepatocyte hypertrophy.[27] This highlights the role of systemic factors contributing in hepatocyte hypertrophy.

The liver's response to a PHx is divided into two main phases. The first phase occurs between days 1-3 and is termed the "inductive phase" (Figure 2A). During this phase hepatocytes undergo proliferation. This proliferative response peaks at 36 hours and goes back down at 72 hours.[28-30] The "angiogenic phase" is the next phase which occurs, from day 4 to 8, where non-parenchymal cells proliferate, returning the liver to its normal mass and function (Figure 2B). Non-parenchymal cells have an essential role during these phases of regeneration, which will be discussed in more detail below.

THE MOLECULAR RESPONSE AFTER A PHx

The ability of the liver to know when to start and stop regeneration has puzzled scientists for years. However, certain factors have been shown to be necessary for regeneration post PHx. For example, Interleukin-6 (IL-6) and the bile acid receptor, FXR, have been shown to be essential for regeneration.[31,32]

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When the genes for IL-6 or FXR are knocked down, there is a higher mortality rate post PHx compared to their respective wild-type counterparts. In addition, assessment of proliferation through BrdU staining shows a poor proliferative response in hepatocytes. However, there is no change in non-parnechymal cells such as Kupffer cells, and endothelial cells, suggesting that non-parenchymal cells do not need IL-6 for this response.

According to transplantation studies, hepatocytes appear to have intrinsic regenerative mechanisms that are species-specific. For instance, transplantation of rat hepatocytes into mice liver, which later are subjected to PHx, has shown irregular proliferation kinetics. Rat hepatocytes become BrdU+ 24 hours later, as expected while mouse hepatocytes express BrdU 32 hours later.[33] Thus, even with the change in cellular environment, rat hepatocytes stay true to their typical response to a PHx. This suggests that hepatocytes have a certain level of autonomy when it comes to regeneration and highlights the intrinsic capability of hepatocytes rather than micro-environmental niche effects.

An alternative mechanism to liver regeneration involves a group of cells termed "Facultative Stem Cells" (FSCs) or "oval cells". FSCs were first described in rat studies that involved exposure to several carcinogens that are known to be toxic to the liver.[34] In rats it has been shown that these cells appear when hepatocyte proliferation is impaired but they are also observed in mice even with hepatocyte proliferation. However, the appearance of oval cells or impaired proliferation is not observed when rodents undergo a PHx without any chemical intervention. Further discussion of FSCs is beyond the scope of this review. Although, it is evident that the liver's resiliency comes from the multiple avenues of regeneration at its disposal.

LIVER SINUSOIDAL ENDOTHELIAL CELLS (LSECs)

LSECs are shown to regulate the temporal response of liver regeneration post-PHx. Angiopoietin 2 (Ang2), is an angiogenic protein that is down-regulated during the inductive phase,[30] which is associated with decreased TGF-β, an anti-proliferative factor, and increased expression of cyclin D1, thus boosting hepatocyte proliferation (Figure 2C). In the angiogenic phase, Ang2 levels increase, and subsequently promotes increased VEGFR2 and Wnt2 expression and proliferation of LSECs initiates[29] (Figure 2D).

The liver vasculature has varying responses to whether there is an acute or chronic injury. During an acute insult, there is up-regulation of CXCR7 by LSECs and increase in CXCR4, which together induce transcription factor inhibitor of DNA binding 1 (Id1).[28] This induces production of Wnt2 and HGF, which are pro-regenerative angiocrine factors and triggers regeneration. The essential role of CXCR7 was shown when deletion of CXCR7 in LSECs through an inducible system resulted in a poor regenerative response due to an impaired ID1 mediated production of angiocrine factors.[28] (Table 1)

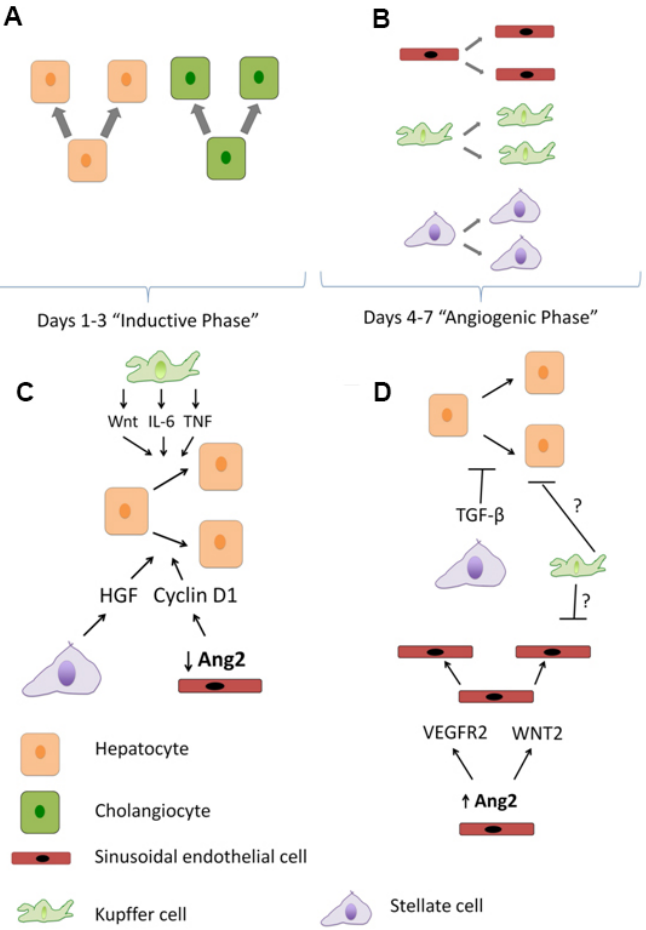

Figure 2: The proliferation kinetics and main signalling pathways involved in liver regeneration after a PHx. (A) Proliferation of non-parenchymal cells occurs during the inductive phase. (B) The angiogenic phase involves proliferation of non-parenchymal cells. (C) Role of non-parenchymal cells during hepatocyte proliferation in the inductive phase. (D) Role of non-parenchymal cells in inhibiting hepatocyte proliferation arrest and regeneration in the angiogenic phase.

Liver Lineage	Signalling pathway	Reference
Foregut Endoderm	Wnt/β-catenin and FGF4 suppressed	18
Hepatoblast	FGF, BMP	35,36
Hepatocyte	Wnt/β-catenin	20,37
Cholangiocyte (Bile duct cell)	Notch	38,39

Table 1: Signalling pathways involved in liver development.

MACROPHAGES

The powerful role macrophages play in regeneration has been shown in organisms such as zebrafish, which depend on these cells to regenerate their fins, and portions of the heart. In addition, macrophages are required for limb re-growth in salamanders.[40] The liver is known to have the highest concentration of resident macrophages of any organ. Both Kupffer cells and recruited monocyte-derived macrophages have been impli-

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cated in liver regeneration after a PHx.[41] When macrophages are ablated using liposomal clodronate followed by a PHx there is a delayed proliferative response from hepatocytes and the size of the remnant liver at 96 hours post-surgery is significantly less in Kupffer cell depleted rats.[41] This suggests that cytokines and growth factors secreted by macrophages are important for proliferative responses. Expression of key cytokines involved in liver regeneration are also down regulated at the mRNA level, this includes, IL-6, IL-10, TNF, HGF, and TGF-β1 at 4 hours post-PHx. The temporal defect in liver regeneration due to the absence of Kupffer cells may be associated with a lack of Wnt ligands that promote Wnt/β-catenin signaling in hepatocytes. When there is macrophage specific knockdown of the gene Wntless and PHx is performed a temporal deficiency in liver regeneration is observed.[42] There is a 1/3 drop in S- phase hepatocytes and hepatocyte mitosis was observed in Wls-MKO mice 40 hours after PHx. This was associated with a reduction in β-catenin-TCF4 complex and Cyclin-D1 expression at 40 hours, highlighting a role for β-catenin mediated TCF transcription factor in this process.[43] These findings suggest that Kupffer cells are essential for initiating hepatocyte proliferation in a timely manner through secretion of Wnt ligands. Other factors thought to be important for hepatocyte proliferation is interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Mice deficient in either IL-6 or TNF-α receptor type 1 showed impaired hepatocyte proliferation 40 hours post-surgery and higher mortality. (Table 2)

STELLATE CELLS

In a healthy liver, Hepatic Stellate Cells (HSCs) are in a quiescent state and store lipids such as Vitamin A. HSCs encompass approximately 5-8% of cells. Upon chronic liver injury, impaired hepatocytes and immune cells secrete factors that cause HSCs to become proliferative and differentiate into myofibroblasts.[10] These myofibroblasts are well known to be key producers collagen 1 and promote fibrosis.[49] Thus, it seems they are associated with an undesirable outcome in liver injury. However, it is also suggested that HSCs may have pro-regenerative properties as well. Spatially, the majority of HSCs reside in the Canals of Hering, a suggested stem cell niche in the adult liver.[46] More importantly, they are known to produce factors associated with regeneration such as HGF, Notch and hedgehog ligands. HSCs isolated from the early phase of regeneration in rats showed high levels of HGF in conditioned media. Furthermore, it has been argued that HSCs express the stem/progenitor cell marker CD133+ and are able to differentiate into hepatocyte-like cells with certain cytokines.[47] A lineage study was done on HSCs using a Glial Fibrillary Acidic Protein (GFAP) promoter and a Green Fluorescent Protein (GFP) reporter gene showing that after a diet-induced injury GFP+ cells proliferate and express progenitor markers cytokeratin 7 and 19.[48] Afterwards, GFP+ hepatocytes were observed suggesting that HSCs gave rise to progenitor cells that went on to differentiate into hepatocytes. They show that HSCs may produce hepatocytes *via* mesenchymal to epithelial transition.

HSCs play an essential role during liver regeneration as their regulatory effect includes stopping regeneration. They secrete factors that arrest regeneration once the appropriate mass is achieved. The dominant arresting factor is TGF-β, which HSCs are the main producers of in the liver. In mice with the gene Foxf1 knocked down, the stellate cells were unable to become activated and impaired liver regeneration ensued along with diminished notch-2 production, which promotes regeneration of biliary epithelial cells.[50] Furthermore, in rats with 2-AAF/PHx injured livers and given L-cysteine in their diets, to impair stellate cell activation, there was abnormal regeneration due to poor progenitor cell response.[51] Thus, HSCs appear to have a temporal role in regulating the regenerative response of the liver. Initially, they promote regeneration through secretion of growth factors and then put on the brakes once the normal weight and function is achieved.

THE CRITICAL ROLE OF HEDGEHOG SIGNALING

The importance of Hedgehog (Hh) signaling goes beyond just development as it is up regulated during regeneration after PHx. When Hh signaling is blocked after a PHx, *via* cyclopamine, there is reduced expression of numerous progenitor markers such as α-fetoprotein (AFP), Factor-inducible 14

	Role in liver regeneration	Reference
Hepatocyte	Hyper proliferative response post-PHx	25
Cholangiocyte (Bile duct cell)	Hyper proliferative response post-PHx	38,44
Sinusoidal endothelial cell	Spatiotemporal regulation in proliferation kinetics of hepatocytes and endothelial cells	28-30
Kupffer cell	Secrete wnt ligands that control hepatocyte proliferation in a timely manner, wnt3a secretion promotes differentiation of hepatic progenitor cells into hepatocytes.	41,45
Stellate cell	Secrete factors that promote and stop hepatocyte proliferation. May give rise to hepatocytes through MET, Secretion of Notch ligands promotes differentiation of hepatic progenitor cells to cholangiocytes.	46-48

Table 2: Contribution of different cellular components of the liver during liver regeneration.

(Fn14), and cytokeratin 19 at the mRNA and protein level.[52,53] Furthermore, proliferation of hepatocytes was impaired as BrdU incorporation decreased by 90% in hepatocytes and 40% in ductular cells.[52,53] The final outcome of this treatment shows a higher mortality in comparison with the control treated group. This highlights the importance of Hh signaling pathway in liver regeneration. It is still not clear which cell type needs activation of the Hh signaling pathway during liver regeneration, which can be further elucidated in cell lineage studies.

CLINICAL INSIGHTS INTO LIVER REGENERATION

The human liver, like in rodents, undergoes a hyperproliferative response after a PHx.[54,55] However, because the PHx model in animals, when done with precision, is relatively "clean" it does not fully recapitulate what is observed in the context of human liver disease, where significant inflammation, necrosis, and fibrosis are commonly observed.

In humans, outcomes of hepatectomy have improved over time. However, post-hepatectomy liver failure is still one of the most fatal complications of hepatectomy and occurs in up to 10% of cases. The ability of the remnant liver to regenerate after hepatectomy is the main factor in determining morbidity and mortality. If the remnant liver is less than 20%, liver function is impaired and could lead to post-resection liver failure.[56,57] Due to a scarcity in treatments for numerous liver conditions, liver resection remains the sole remedy,[54-57] despite the high concern for morbidity and mortality.[58,59] Investigating the pro-regenerative aspects of the cell types discussed above may assist in enhancing the recovery and survival of patients' post-hepatectomy and possibly after trauma, such as a severe burn.[60] Thus, despite the divergence, the compensatory response after liver resection is clinically essential and provides a great model to learn about growth and regeneration. A better understanding of how cells in the liver interact and respond to their microenvironment will give us the ability to pinpoint aberrant healing and develop novel therapies to treat liver disease.

FUTURE OUTLOOK

The regenerative capacity of the liver is unquestionable. Whether a single or several cell type(s) give rise to new hepatocytes during liver regeneration is not yet well defined. While it is believed that hepatocytes undergo hypertrophy and proliferate to regenerate the liver, it is not clear whether all hepatocytes are able to proliferate. Can a group of hepatocytes have higher capacity to proliferate? Are these hepatic progenitor cells? In addition, the majority of liver regeneration studies using the PHx model focus on how regeneration is initiated and what factors promote it while missing out on how it is stopped once regeneration is complete. Thus, future studies need to focus more on cell specific studies through lineage tracing to address the plasticity of liver cells and their fate during regeneration. Furthermore, a better understanding of how liver regeneration is terminated and the discrepancies between the PHx model in rodents and what is observed in the clinic need to be taken into consideration.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Research

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Post-Thyroidectomy Hypocalcemia: Timing of Discharge Based on Serum Calcium Levels

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ABSTRACT

Purpose: The study concerns about the evaluation of Calcium serum levels in patients who underwent total thyroidectomy. Our previous experience underlined how patients who had levels of serum Calcium more than 9 mg/dl at the first day after surgery, did not show Hypocalcemia in the next days, so that this value could be considered a good cut-off for the decision of an early discharge. With regards to this experience, the aim of our current study was to confirm the effective feasibility of an early discharge based on the levels of serum Calcium at the first post-operative day.

Patients and Methods: Our study included 102 consecutive patients (82 F; 20 M, age with a range between 14-78 year sold, average 52.6) that were submitted to total thyroidectomy in the years 2010 to 2014, performed by the same operator and all done with sutureless technique (Ligasure precise©) We classify hypocalcemia, according to their normal range (8.6 to 10.4 mg/dl), in mild (not less than 7.6 mg/dL), moderate (between 7.5 mg/dL and 7 mg/dL) and severe (less than 7 mg/dL) We classified the normal range of serum Calcium between 8.6 mg/dl and 10.4 mg/dl. Patients that showed levels of serum Calcium under this limit (<8.6 mg/dl) were treated with 6 fials of Gluconate Calcium 40 mEq in 500 ml of saline solution NaCl 0.9% i.v. (one per day), until the return to the normal range. Patients who had serum Calcium levels more than 9 mg/dl at the first post-operative days, and did not have other complications, were discharged at the same day and revaluated after 7 days.

Discussion and Conclusion: Moreover our study has been useful to confirm what we observed in the previous experience, that levels of serum Calcium more than 9 mg/dl at the first post-operative day can be considered a feasible cut-off to exclude the appearance of hypocalcaemia in future.

Therefore, according to our results, we assume to propose an early discharge for the patients who have serum Calcium levels more than 9 mg/dl, asking them to come back for controls one week after discharge.

KEYWORDS: Surgery; Calcium; Thyroid gland.

ABBREVIATIONS: iPTH: intact Parathormone; POD: Postoperative day.

INTRODUCTION

Surgery is a therapeutic strategy for the treatment of different thyroid diseases (multinodular goiter, tumors, lymphomas). The presentation of thyroid gland pathologies can vary from specific symptoms (for the overproduction of thyroid hormones), to an asymptomatic growth of the gland, entirely or as a nodule, so that they are accidentally disgnosed.[1]

Once the pathology is diagnosed, surgical treatment is necessary to remove the gland partially or totally. Patients undergoing total resection need to be hospitalized to evaluate the possible onset of complications that should be treated promptly. Possible complications related to thyroid surgery mainly include:[2,3]

- Bleeding and hematoma
- Recurrent laryngeal nerve injury
- Postoperative hypocalcemia

Regarding to bleeding, it is now clear that the fatal ones may occur 4-6 hours after surgery, and in general, exceptionally a few hours later, rarely after 24 hours.[4]

The unilateral or bilateral recurrent lesions usually appear within 24 hours, in this way early diagnosis and treatment are usually performed; they represent contraindications to early discharge.[5,6] With regards to the post-operative hypocalcaemia, it is an uncommon occurrence although the incidence and the cause are not yet clear.

Its incidence in large case studies is variable: transitional hypocalcemia can vary from 1.6% to 68%, while permanent hypocalcemia varies from 0, 4% to 33%.[7-10] Traditionally, the period of observation in patients who underwent total thyroidectomy is at least 3 days (72 hours).[11]

The trend of some specialized centers was, in selected cases, to reduce the period of observation to 24 h (One Day Surgery).[12,13] Our previous experience underlined how patients who had levels of serum Calcium higher than 9 mg/dl at the first post-operative day, did not show Hypocalcemia in the next days;[14] for this reason this value could be considered a good cut-off for the decision of an early discharge.[1]

With regards to this experience, the aim of our current study was to confirm the effective feasibility of an early discharge based on the levels of serum Calcium at the first post-operative day.

MATERIALS AND METHODS

Our research included all patients undergoing total thyroidectomy from January 2010 until December 2014. Surgeries were all performed by the same operator and all with suture less technique (Ligasure precise©). After surgery, all patients were treated with Levothyroxine 100 mg (1 cp per day) and Calcium Carbonate 300 mg (2 cps per day). We measured the serum Calcium at the first post-operative day and in next ones until discharge, and successively 7 days after discharge.

We assumed the normal range of serum Calcium is between 8.6 mg/dl and 10.4 mg/dl. Patients that showed levels of serum Calcium under this limit (<8.6 mg/dl) were treated with 4vials of Gluconate Calcium (40 mEq) in 500 ml of saline solution NaCl 0.9% *intra venus* (*i.v.)* (one per day), monitoring the Serum Calcium levels daily. The treatment was suspended when the Serum Calcium levels were at the normal range.

Patients who had serum Calcium levels more than 9 mg/dl at the first post-operative days, and did not have other complications, were discharged the same day and revaluated after 7 days.

RESULTS

Our study included 102 consecutive patients (82 F; 20 M, age ranged between 14-78 years old, average 52.6).

Post-operatively pathological examinations are reported in Table 1.

	2010	2011	2012	2013	2014	TOT
MNG	14	16	9	8	9	**56**
Toxic	2	5	0	2	1	**10**
Recurrent	1	3	2	2	0	**8**
Dipped	0	2	2	2	0	**6**
Follicular CA	0	0	0	3	0	**3**
Hurtle	0	0	1	0	1	**2**
Papillary CA	4	2	7	10	9	**32**
Atypical Adenoma	2	0	0	1	4	**7**
Medullary CA	0	1	1	0	0	**2**
Lymphoma	0	0	0	0	0	**0**
TOTAL	20	19	18	22	23	**102**

Table 1: Pathological examinations results after surgery (MNG: Multi Nodular Goiter; CA: cancer).

Out of 102 patients who underwent total thyroidectomy, hypocalcemia was observed in 18 cases (16%), out of which 15/102 cases (14.7%) were transitional, while 3/102 cases (2.9%) were permanent.

Regarding to the 18 patients presenting hypocalcemia, in 7 patients it occurred at the first Postoperative day (POD) (38.8%), in 4 patients at the second POD (22.2%), in 6 patients at the third POD (33.3%), in 1 patient at the fourth POD (5.5%).

At the first POD, 71 patients out of 102 had serum Calcium levels higher than 9 mg/dl (Table 2). These patients were discharged the same day, between 24 and 30 hours after surgery (average 26.7 hrs).

Serum Calcium at 1st POD	Patients	%
9-9.5	45/102	44%
9.6-10	23/102	22%
10.1-10.4	3/102	3%
Total	71/102	69%

Table 2: Serum Calcium values at the first post-operative day.

These patients were examined after 7 days from discharge. No one of them reported symptoms of hypocalcemia. Values of serum Calcium after 7 days were all in the normal range (8.6-10.4 mg/dl). Twenty patients (28%) had serum Calcium between 8.6 mg/dl and 9 mg/dl, 31 patients (43.7%) between 9.1 mg/dl and 9.5 mg/dl, 18 patients (25.3%) between 9.6 mg/dl and 10 mg/dl, 2 patients (2.8%) between 10.1 mg/dl and 10.4 mg/dl (Table 3).

Levels of serum Calcium	Number of patients	Percentage
<8.6	0	0%
8.6-9	20	28.2%
9.1-9.5	31	43.7%
9.6-10	18	25.3%
10.1-10.4	2	2.8%

Table 3: Values of serum Calcium after 7 days from discharge.

DISCUSSION

The current research was focused on the feasibility of an early discharge in patients who underwent total thyroidectomy, based on the absence of complications and the levels of serum Calcium. Many papers in the International literature describe different features to predict the occurrence of hypocalcemia in patients who have undergone total thyroidectomy.

Al Qahtani, et al.[15] proposes to use as an early predictor of hypocalcemia the intact Parathormone (iPTH) essay 1-hour, 6-hourand 24-hours post-thyroidectomy. Also Seo[16] underlines how iPTH essay can be used for evaluating the possible appearance of hypocalcemia, resulting in a sensitivity and specificity of 83.4% and 100% respectively.

On the other hand, some authors, accepted Serum Calcium assay as an early predictive factor of hypocalcemia,[17,18] measuring iPTH assay to 4-6 weeks and 1-year post-thyroidectomy controls.[18]

Basing on our experiences, we assume Serum Calcium measurement as a good predictive factor of hypocalcemia, considering its reliability, easier feasibility and low costs of this exam. Besides, our study underlines that the first post-operative days are crucial for an early discharge of the patient (24-30 h), confirming what we already experienced in our previous research.[14]

Moreover, we confirmed that levels of serum Calcium more than 9 mg/dl at the first post-operative day, in patients treated with Calcium Carbonate 300 mg (2 cps per day) from the same day after surgery and the following day, can be considered a feasible cut-off to exclude the appearance of hypocalcemia, as we observed in the previous experience.[14]

Therefore, according to our results, we propose serum calcium measurement as a predictive factor of hypocalcemia in patients who have undergone total thyroidectomy, and to propose an early discharge for the patients who have serum Calcium levels more than 9 mg/dl, prescribing a medical examination one week after discharge.

CONFLICTS OF INTEREST

All authors declare that they have no conflicts of interest.

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AUTHOR CONTRIBUTION

All authors contributed significantly to the present research and reviewed the entire manuscript.

SP: Participated substantially in conception, design and execution of the study and in the analysis and interpretation of the data; also participated substantially in the drafting and editing of the manuscript.
SR: Participated substantially in conception, design and execution of the study and in the analysis and interpretation of the data.
MA: Participated substantially in conception, design and execution of the study and in the analysis and interpretation of the data.
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Research

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A New Prosthesis in Inguinal Hernia Repair: Results of a Pilot Study

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ABSTRACT

Purpose: Prosthetic reinforcement is the gold standard in inguinal hernia repair. One-third of patients complain of post – surgical pain due to irritation and inflammation caused by the mesh and methods of fixation; 4-10% of these will experience severe chronic pain. We performed a prospective single arm study for the assessment of post-operative pain after inguinal hernia repair with a new self-gripping hernia prosthesis.
Methods: From December 2011 to December 2013, 44 consecutive patients with primary oblique inguinal hernia underwent to inguinal hernia repair with Proflor™ (Insightra). All patients were preoperatively evaluated by ultrasound and the defect size was < 2 cm. Visual Analog Scale (VAS) was assessed at 7 days and 3-6 months. All patients were included in ultrasound follow up at 7 days and 3-6-12-18-24 months.
Results: No sutures or other fixation systems have been used.According to the VAS scale pain was reported in a range from 1 to 3 during the first week. No peri-operative complications occurred. 10 post-operative complications was reported: 3 hematomas (6.8%), 1 ecchymosis (2.2%), 2 seroma (4.5%), 4 hypoaesthesia (9.1%). None of total implants delivered dislodged, as confirmed bythe ultrasounds.
Conclusions: Operative and post-operative complication rates were comparable to the literature; chronic pain did not occur. The use of this new prosthesis, which through its design allows fixation without sutures, could be an alternative method to decrease chronic pain after inguinal hernia repair. We acknowledge that further studies are needed.

KEYWORDS: Inguinal hernia; Chronic pain; Self-gripping; Proflor™.

ABBREVIATIONS: VAS: Visual Analog Scale; IASP: International Association for the Study of Pain; QoL: Quality of Life.

INTRODUCTION

Hernia repair is one of the most common surgical procedures performed in the United States, with 800,000 operations each year.[1] The new prosthetic materials have significantly improved outcomes for many patients. Inguinal hernia repair historically was challenging and recurrence rates were high. To reduce the incidence of recurrence rate, Lichtenstein tension free mesh repair or similar procedures were introduced into open inguinal hernia. This showed a dramatic reduction in recurrence rates.[2] However, mesh fixation with sutures, to avoid dislocation has been reported in the literature as a cause of chronic pain and discomfort. According to the International Association for the Study of Pain (IASP) chronic groin pain was "groin pain reported by the patient at or beyond 3 months following inguinal hernia repair.[3] Post-operative pain may be incapacitating and can dramatically affect quality of life; the reported incidence of chronic pain 1 year after hernia repair varies from 0.7 to 28.7%.[4] Management of chronic groin pain constitutes a challenging issue for the clinician, often more challenging than deal-

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ing with recurrence. According to the literature, perioperative nerve damage, postoperative fibrosis, and mesh related fibrosis are the main reasons for chronic groin pain.[4,5] In attempts to reduce it, researchers have tried various surgical techniques and materials.[6,7] Therefore a novel technique for a diminished rate of post-operative chronic pain was developed. We used a new self–gripping 3-D prosthesis for inguinal hernia repair, which does not require suture point fixation.

PATIENTS AND METHODS

From December 2011 to December 2013, we performed a prospective single arm study for the assessment of post-operative pain after inguinal hernia repair with a new self-gripping mesh (Freedom Proflor™; Insightra) (Figure 1).

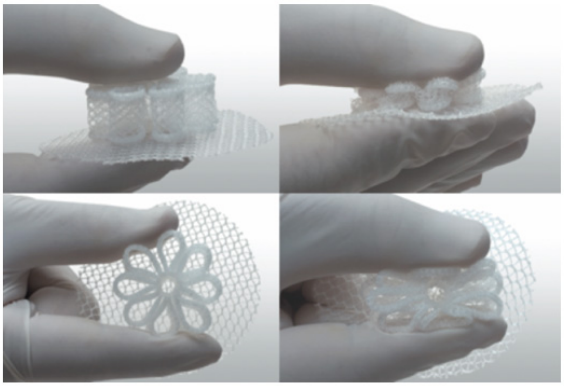

Figure 1: 3D polypropylene implant with a multi-lamellar central core with a welded pre-peritoneal disc (Freedom Proflor™; Insightra).

The study was approved bythe local ethics committee, informed consent was provided by all patients. According to Nyhus classification,[8] 44 consecutive patients with primary unilateral inguinal hernia stage I-IIIa were included. We did not included patients ASA IV-V, BMI>35 and stage IIIb or IV. Characteristics of the patients are shown in Table 1.

Total patients	N=44
Median (range)/Age (years)	51,08/(32-68)
Sex Ratio (M/F)	42/2
Median BMI (Kg/m²)/Range	27.4/(19.4-35)

Table 1: Patient characteristics.

Ultrasound scan was postoperatively performed in all patients after 7 days, 3 months and after 6 months, to detect any early recurrence, shrinkage or dislocation. Patients were invited to the outpatient setting 3, 6, 12, 18 and 24 months after surgery. The primary end point of this study was to evaluate the incidence of postoperative chronic pain defined as any pain reported by the patient beyond 3 months post surgery, according to international association of the study of pain (IASP);[3] pain intensity was categorized as mild (occasional discomfort or pain not interfering with daily activities), moderate pain (discomfort or pain occasionally interfering with daily activities) and severe pain (discomfort or pain interfering with daily activities) with long post-operative follow up at 24 months.

In agreement with Bodian CA, et al,[9] visual analog scale (VAS) was used to evaluate chronic pain in which score of 0=pain, score 1 to 3=mild pain, score 4 to 6=moderate pain, score 7 to 9=severe pain, score 10= unbearable pain.

SURGICAL TECHNIQUE

The surgical technique at the Day Surgery of the University Hospital of Rome Tor Vergata can be considered a variant of the technique proposed by Lichtenstein,[10] by the use of a self-fixing, three-dimensional implant.

Inguinal hernia repairs were performed using the new prosthesis by the same surgeons with an experience of more than five procedures to eliminate bias of a learning curve. All patients received local or locoregional anesthesia (Naropine 10%) and prophylactic antibiotic (1 × 2 g Cefazolin). In all procedures an oblique 4-7 cm incision was made overlying the inguinal canal. The external oblique aponeurosis was opened and blunt dissection was used to separate the sac from the cord. The hernia sac was ligated and resected and the pre-peritoneal space was prepared by blunt finger dissection of the tissue planes. A polypropylene implant consisting of a “flower shaped” central core with a pre-peritoneal disc was used as per the manufacturer’s instructions for use. The implant was placed with a proprietary delivery device, which compressed to flower during insertion. The implant was released and adjusted to sit in the correct anatomical space. No suture point or other method of fixation was used. The characteristics of hernia size and the dimension of implant used were reported in Table 2.

Type of hernia (Nyhus)	Number Pieces	Mesh size core (mm)	Mesh size disc (mm)
I	5	25	60
II	37	40	70
IIIa	2	40	70
Defect size (cm)			
<1,5 cm	5	25	60
1,5-3 cm	39	40	70

Table 2: Hernia size and implant use.

RESULTS

We investigated short-term (within 7 days from surgery) and long-term complications (more than 3 months after surgery) in 44 patients, with particular attention to chronic postoperative pain. The median follow-up was 17.65 months (range, 3-24). One patient was lost to follow-up after 3 months for an unrelated death.

There were 10 cases of early complications (22.7%): 3 cases of hematoma (6.8%), 1 ecchymosis (2.2%), 4 inguinal

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hypoaesthesia (9.1%), 2 seromas (4.5%), no case of infection occurred. At 1 month all early complications resolved spontaneously. All patients were followed closely on an outpatient basis and have not been necessary medical procedures invasive. Hematoma and bruising were resorbed independently, serom as were small in size, we decided the only clinical observation and these are reabsorbed independently. Mild acute post-operative pain was present in 40 patients (90.1% of the sample) with a median duration of 3 days (range 1-7 days).

According to the VAS score, pain reported during the first post-operative week ranged from 0 to 3 (Mean 1.09, SD 0.98) (Table 3). In all patients acute pain was completely resolved within 7 days after surgery with the use of 1 g of paracetamole.

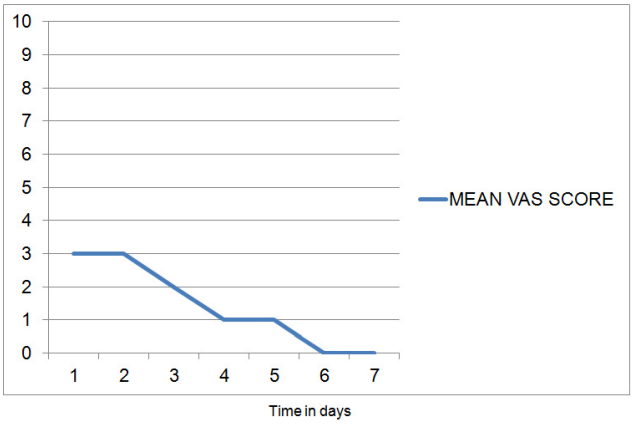

Table 3: Mean visual analog scale (VAS) pain scores in the first week after Proflor™ inguinal hernia repair.

Late complications investigated were: recurrence, testicular atrophy, and chronic postoperative pain (Table 4).

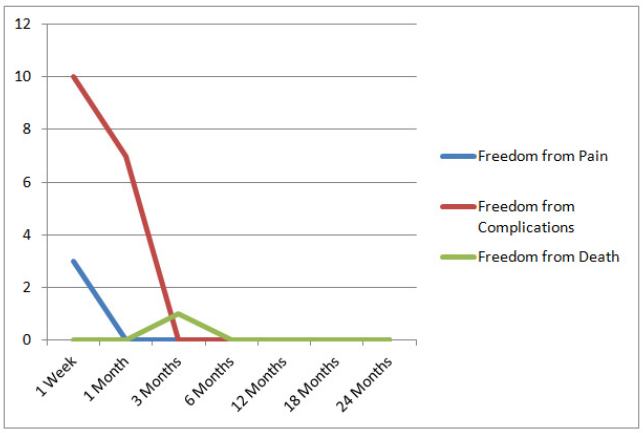

Table 4: Number of patients with adverse event during the follow-up.

All patients underwent clinical and instrumental (ultrasound and Doppler ultrasound) within 7 days, 3-6-12-18-24 months. The use of post-operative ultrasound served for the assessment of the correct positioning of the prosthesis and any dimensional changes linked to the infiltration of fibrotic, contracting scar tissue (Figures 2 and 3). No shrinkage or migration of mesh was found from the first control until 24 months. The red line in Figure 3 shows no dimensional change in the mesh core, it results 39.7 mm using an implant core of 40 mm.

The ultrasound examination showed no recurrence or testicular atrophy in any patient.

The onset of chronic post-operative pain was evaluated at 3-6-12-18-24 months after surgery through administration of the VAS score (Table 5). At the minimum follow-up of 3 months after surgery none of the patients felt pain. No cases of chronic pain were detected at follow-up of 3-6-12-18-24 months after surgery (median follow-up was 17.65 months).

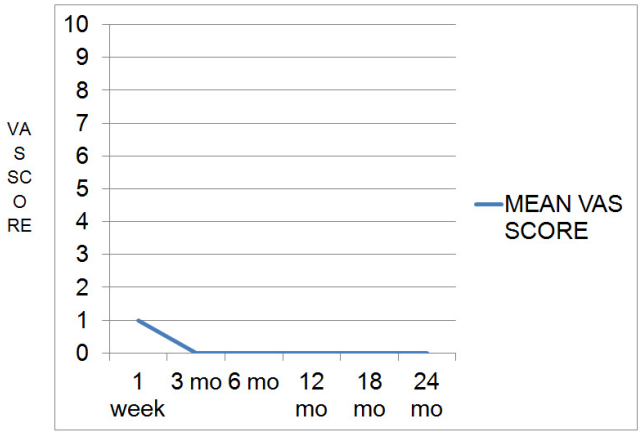

Table 5: Mean visual analog scale (VAS) pain scores in 2 years after Proflor™ inguinal hernia repair.

DISCUSSION

The evolution of prosthetic hernia repairs can be traced back to more than three decades ago;[11] the concept of tension-free hernioplasty has achieved long-term success with low recurrence, short hospitalization and decreased preoperative pain.[10] Although the Lichtenstein repair is known as a safe and easy technique with a low morbidity rate, in several publications, high rates of postoperative inguinal chronic pain have to be recognized.[12] Unfortunately the definition of chronic postoperative pain, is not clear: it can include neuralgia (e.g. from the ilioinguinal and/or genitofemoral nerve), slight to serious inguinal pain, paresthesia, and dysaesthesia.[13,14] Because of these different definitions of pain, comparison between published results is highly problematic. Furthermore, study populations are often heterogeneous, comprising of both open and laparoscopic repairs, primary and recurrent hernias, and varying lengths of follow-up assessment.[15,16] In our study, postoperative pain is conventionally divided into acute and chronic, depending on which will be resolved during the first 3 months after surgery; chronic postoperative pain defined as any pain reported by the patient beyond 3 months post surgery, according to the international association of the study of pain (IASP).[5]

In a review of Poobalan AS, et al. an incidence of chronic pain in hernia surgery from 0% to 2% was reported

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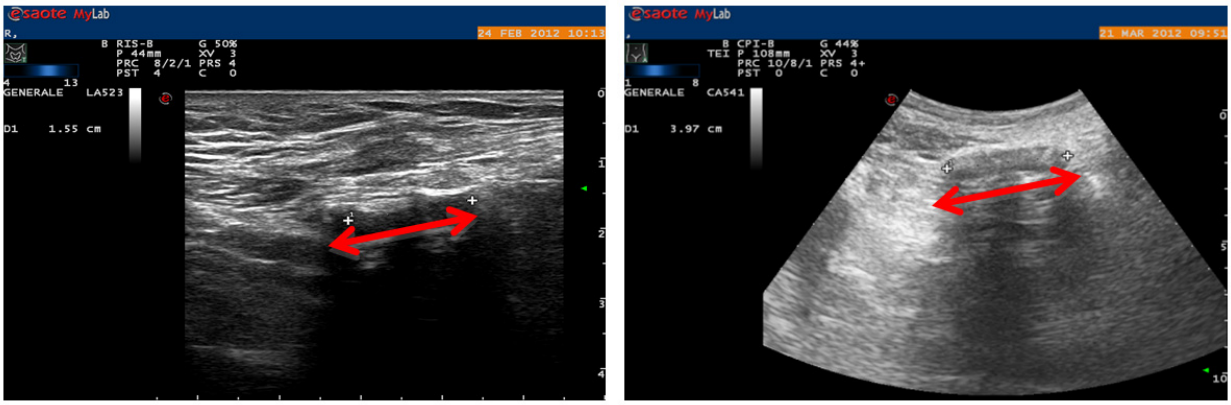

Figures 2 and 3: The ultrasound shows the correct position of the prosthesis after 6 months. The line shows the dimension of the prosthesis core: 39.7 mm.

in centers specifically dedicated to hernia surgery. Instead, in public hospitals or universities, values refer to much higher incidences (12-37%).[17] An important publication of the Danish Hernia Data Base Group reports an incidence of chronic pain at 12 months of 28.7%, with 11% considered severe disabling type of pain.[18] Other recent studies confirm an incidence of a high post-operative pain, suggesting the distinct importance of the problem: 7.6%,[3] 31%,[4] 19.7%.[5] The variability of this data is influenced by the different methods of defining pain. However, few of these studies have a long post-operative follow-up and a population large enough to give clear results.

Several risk factors have been identified to play a crucial role in the development of chronic pain, including low patient age, female sex, high preoperative and immediate postoperative pain scores, and surgery for recurrent hernia.[18] However, the long-term influence of the different surgical approaches to the groin and the presence or absence of a prosthetic mesh on long-term pain is not clear.[17]

There are many factors considered responsible for the onset of chronic postoperative pain: the experience of the surgeon, re-do surgery, damage to the nerves and the position of the mesh.[17] Many authors believe the use of prostheses and the open technique may play a role in the onset of chronic postoperative pain;[18] others exclude both of these factors;[19] still others believe that the tension-free technique is associated with a lower risk of chronic pain compared to a sutured tissue to tissue repair.[20]

Because of the variability of these findings, it is very difficult to find a common aetiology for pain. It is believed that the presence of prosthesis may contribute to the onset of pain. It has been hypothesized that, by varying the position of mesh placement, the composition of the materials or methods of fixation; we can reduce post-operative pain in inguinal hernia surgery.[21] Of course, the accuracy of dissection and damage to delicate structures may also influence the postoperative course and influence the onset of chronic pain.[5] Polypropylene flat mesh may be associated with pain and discomfort as it generates a profound inflammatory response, which results in negative, fibrotic scar formation, increased rigidity and stiffness of the abdominal wall, and shrinkage of the biomaterial with time. The search for the ideal prosthetic biomaterial has been a longstanding issue with debate over simple versus composite biomaterials and lightweight *versus* heavyweight meshes. The characteristics of the ideal prosthesis are well defined: large overlap of mesh, strong, flexible, low specific weight, biologically inert and able to be incorporated into the tissues with large pore size.

In our practice, the Proflor™ prosthesis has several characteristics of these "ideal" implants: it is made from inert non-absorbable polypropylene, is self-fixating, has a three-dimensional structure which allows a dynamic behaviour, lightweight, large pore structure; and most importantly, moving with the muscular structures through its dynamic design. This results in a different biological response to flat meshes: rapid incorporation, less inflammatory response, regeneration of tissue instead of the growth of a fibrotic scar.[22]

Several studies have shown that, at the onset of the hernia pathology, there is a degeneration of the tissues of the inguinal region, leading to weakness of the groin.[1-3]

Most of the techniques described today do not take into account the pathophysiology of inguinal region and, because they use static systems do not comply with the dynamics of the abdominal wall in the inguinal region. The implants used to repair the hernia defect have what is considered a "static behaviour" and are often fixed in various ways to the muscles, and often on top of sensory nerves. This goes against the mobility of the muscles of the groin potentially causing an intense inflammatory response that may contribute to the genesis of chronic pain after surgery. The device we used in this prospective study adapts to the movements of the inguinal region, which is quite unique. Our dynamic ultrasound studies on these patients demonstrate a complete integration of the implant into the groin tissues with apparently healthy tissue in the area where the hernia was. This appears to be in line with previous animal studies.[23]

In our sample, the incidence of chronic pain was shown

to be 0%. The difference between results in terms of chronic pain compared to data in the literature might be due precisely to the use of this new prosthesis described above. The absence of fixation, combined with a better quality of dynamic scar seems to reduce chronic pain significantly.[24] Previous pre-clinical work with the device demonstrates that being dynamic combined with the absence of additional fixation sutures, results in a reduced inflammatory response and non-fibrotic scar.[22] For this reason, all of our patients underwent clinical and instrumental (ultrasound and Doppler ultrasound) investigation within 7 days, 3-6-12-18 months and 2 years after surgery. The use of ultrasound served for the assessment of the correct positioning of the prosthesis post operatively, and over time looked for any dimensional variations implicating shrinkage (Figures 2 and 3). We found it crucial to confirm that there was no shrinkage as has been reported in most meshes. Shrinking fibrotic scars are thought to be partly responsible for the genesis of chronic post-operative pain so we feel the reduction of such scars contributed to lower pain scores in our study.

CONCLUSION

The problem of chronic pain after inguinal hernia repair can be significantly disabling[1] and is poorly accepted by the patient as a result of hernia being a benign disease. This complication may be attributed to the direct involvement of nerves trapped in sutures (neuropathic pain), or mainly a consequence of inflammatory fibrotic response to the placement of a foreign body on top of sensory nerves, or contracting upon delicate inguinal tissues. Despite the small number of patients in this study the results of the study are very encouraging. We saw, as hypothesized, a very low chronic pain score. We think in part as a result of no point fixation, and in part as result of a better integration of the prosthesis. Based on these results we are participating in a major international study that will look at 150 patient's long term with a specific goal at looking how this seeming absence of chronic pain translates into quality of life scores.

COMPETING INTERESTS

The authors declare that they have no competing interests or financial support

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DV: Manuscript preparation, interpretation of data and critical review.
PR: Acquisition data and drafting the manuscript.
GL: Acquisition data and drafting the manuscript.
FDS: Acquisition data and literature review.
GS: Acquisition and processing data.
ADM: Acquisition and processing data.
SE: Literature review and manuscript preparation.
OCB: Literature review and manuscript preparation.
All authors read and approved the final manuscript.

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SURGICAL RESEARCH

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Mini Review

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Management of Adnexal Masses in Children and Adolescent Populations: Advocating for Ovarian Conservation

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INTRODUCTION

When a young girl or adolescent presents to the Emergency Department with acute lower abdominal pain, it is not uncommon for a general surgeon to be consulted, as appendicitis is always top of the differential diagnosis. The management dilemma occurs when imaging reveals an adnexal mass in the setting of an acute abdomen. Historically, surgical management recommendations were for laparotomy with unilateral salpingo-oophorectomy, in an effort to avoid incomplete excision of cancer.[1-3] Laparoscopy has since replaced laparotomy as the surgical method of choice, however ovarian conservation procedures are often not considered unless a gynecologist is present. This goal of this article is to address the importance of ovarian conservation in adnexal masses in children and adolescents.

BACKGROUND

The incidence of adnexal masses in children has been estimated at 2-5 cases per 100,000 patients per year, depending on the series.[2,4,5] The majority of these cases are benign, as malignancy rates have been quoted between 3.7 and 23.5%,[2] however ovarian cystectomy is still only performed in 61.4% of cases.[3] The differential diagnosis of adnexal masses lists both benign and malignant tumors (Table 1). Benign masses include cysts, endometriomas ("chocolate cysts"), mature cystic teratomas (dermoids), cystadenomas (serous or mucinous), ectopic pregnancy, or other benign neoplasms. One must also consider non-gynecological causes of pelvic masses including appendiceal abscess and pelvic kidney. Cysts are most common at 57.9%, with hemorrhagic corpus luteum cysts (26.4%) and follicular cysts (17.1%) being the most common types.[6] Torsion of the ovary or fallopian tube (with or without an associated mass) may lead to edema which can also appear as a mass on imaging studies. Malignant masses include epithelial, germ cell, sex cord, and metastatic tumors. While epithelial ovarian tumors are the most common malignancy when including all age groups, non-epithelial tumors are more common in women under 19 years of age.[6,7] The most commonly found malignancie tumors, specifically immature teratomas and dysgerminomas.[2,6] Women greater than 15 years of age present more commonly with benign masses than those 15 or younger, with rates of malignancy estimated at 4.4 *vs.* 11.1%.[2]

DIAGNOSIS

Although 8-13% of adnexal masses in children and adolescents less than 18 years of age are incidental, the majority of masses are identified due to symptoms. A thorough history and physical exam are an indispensable initial first step in evaluation. An estimated 57-60% of patients with a mass will have abdominal pain, and 22% will have a palpable mass.[2,5]

Additionally, 18% of patients may have menstrual irregularities and a small number

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Benign	Neoplastic	Mature teratoma Cystadenoma (Serous or Mucinous) Fibroma Adenofibroma Thecoma Luteoma
	Non-neoplastic	Follicular cyst Hemorrhagic cyst Paratubal/Paraovarian cyst Endometrioma Torsion Ectopic pregnancy
Malignant	Epithelial	Cystadenocarcinoma (Serous or Mucinous) Brenner Endometrioid Clear cell Borderline (Low Malignant Potential)
	Germ Cell	Gonadoblastoma Dysgerminoma Endodermal sinus tumor Embryonal carcinoma Immature teratoma Ovarian choriocarcinoma
	Sex Cord-Stromal	Sertoli-Leydig Granulosa-Theca cell Gynandroblastoma
	Metastatic	Krukenberg (Gastrointestinal) Breast Endometrial Lymphoma

Table 1: Differential diagnosis of adnexal mass.

may even present with precocious puberty.[5,7] Pelvic ultrasonography, *via* transabdominal and transvaginal approaches, should be considered first line imaging, as it is widely available, low-cost, and non-invasive.[7] Transvaginal approach provides imaging of smaller masses as well as internal characteristics. Sonographic analysis should include largest diameter, gross morphology, and Doppler flow in the ovarian vessels. Internal morphology consistent with a heterogeneous or solid mass is more indicative of malignancy than a unilocular, homogenous cyst.[8]

Serum markers are also used to identify malignancy to help with surgical planning and management; certain markers can help delineate type of tumor as well (Table 2). CA-125, used in monitoring of epithelial ovarian cancer in older women, is limited by the lack of specificity in this age group, as epithelial ovarian carcinomas are rare in children and adolescents. It is elevated in up to 1% of normal reproductive age women, as well as in women with confounding conditions such as endometriosis, first trimester pregnancy, Crohn's disease and pelvic inflammatory disease.[7] Tumor markers that have been shown to be more associated with cancer in this age group include Alpha-fetoprotein (AFP, OR 9.60), Beta Human Chorionic Gonadotropin (βHCG, OR 5.93), and Lactate dehydrogenase (LDH, OR 225).[5,9] Additionally, thrombocytosis has been associated with ovarian malignancy in children and adolescents; as many as 33% of those with a germ cell tumor had thrombocytosis.[10] Most tumor markers can take several days to result and may not be of use in an emergency setting.

Tumor Marker	Associated Malignancy
Ca-125	Epithelial ovarian tumors
AFP	Endodermal sinus tumors
LDH	Dysgerminomas Endodermal sinus
βHCG	Choriocarcinoma Polyembryoma
Inhibin, Mullerian Inhibiting Substance	Granulosa cell tumor

Table 2: Tumor markers.

Surgical excision is recommended for suspicious masses, positive markers, and benign cysts that are symptomatic, persistent beyond 4-6 weeks, greater than 5 cm in greatest diameter or if ovarian torsion is suspected.[4]

MANAGEMENT

The literature provides limited evidence-based recommendations for management of adnexal masses in children and adolescents, although more case series have been published as of late, in both Gynecology and Pediatric Surgery Journals. Historically, surgeons favored laparotomy with unilateral oophorectomy with or without removal of the fallopian tube.[2,3,7,11] Current literature indicates a significant trend over recent decades to-

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wards laparoscopy and ovarian-conserving surgical procedures, such as ovarian cystectomy, in this age group.[12]

Berger-Chen and colleagues assessed the Perspective database and showed that since 2000, use of laparoscopy has increased from 32.1 to 57.9%, although these rates are affected by socioeconomic factors such as African-American race (OR 0.49) and geographic location in the Northeastern United States (OR 0.65).[3] Patients undergoing laparoscopy are 2 times more likely to have cystectomy performed.[3] Presence of a Gynecologist as primary surgeon increases use of laparoscopy and ovarian conserving surgery, as much as 8.7 times for all masses and 15 times for benign masses.[12] Gynecologists are more often involved when the patient is post-menarchal or greater than 15 years of age.[12]

Ovarian conservation is important, as women with a prior oophorectomy have a 3-15% risk of pathology or torsion in the contralateral ovary and more frequently will seek infertility consultation later in life.[12,13] Resistance to ovarian-conserving surgery has several factors contributing including surgeon's fear of malignancy, relative inexperience with adnexal masses, and in the case of ovarian torsion, risk of thromboembolic events and unrecoverable ischemia.[2,11]

To address this dilemma, criteria have been proposed to risk-stratify ovarian masses in order to facilitate the use of ovarian-conserving surgical techniques such as cystectomy.[2,5,7,8,14] These criteria aim to identify masses most likely to be benign and therefore are candidates for laparoscopic surgery with ovarian conservation. Papic and colleagues identified three criteria to isolate benign masses preoperatively, based on ultrasonography and serum markers: 1) maximum diameter less than 10 cm, 2) no solid components present on imaging studies, and 3) normal serum tumor markers, specifically alpha-fetoprotein (AFP, OR 9.60), beta human chorionic gonadotropin (βHCG, OR 5.93), and lactate dehydrogenase (LDH, OR 225).[5] A combined negative likelihood ratio calculated to be 0.01 is highly specific for benign masses, reducing risk of malignancy in the studied sample from an estimated pre-test probability of 20% to 0.25%.[5] Hermans and colleagues applied these criteria post hoc to a cohort of 111 patients with adnexal masses whom had already undergone surgery, resulting in a sensitivity of 40.91% and specificity of 100%. Preoperative application of these criteria would have prevented two laparotomies and seven oophorectomies, indicating that these criteria are sufficiently specific to rule out malignancy, however improving the sensitivity for benign masses may be able to further decrease the incidence of laparotomy and oophorectomy.[2] Rogers and colleagues performed a similar retrospective study, utilizing sonographic but no serum markers, which identified that 100% of malignant masses were greater than 8 cm with and complex on sonography, with a sensitivity of 36%, positive predictive value of 37.1%, and negative predictive value of 100%.[14] Application of these criteria to the retrospective cohort would have reduced open procedures by 40%.[14] A larger series by Oltmann, et al. of 424 patients with surgically treated adnexal masses showed that malignancy was more common in patients age 1-8 years (OR 3.02) with complaints of a precocious puberty (as compared to pain, OR 4.8 and 5.67, respectively), and a heterogeneous or solid mass (OR 6.84 and 10.13) with a maximum diameter of greater than or equal to 8 cm (OR 19.0).[8] Tumor markers were only elevated in 54% of the malignancies in this cohort, and 6.5% of benign masses.[8] These data support using 8 cm as a diameter criterion, but diminish the impact of tumor markers on stratification. It should also be noted that criteria such as these often perform less well when replicated, but a sensitivity between 0.4 and 0.6 can be expected.[15]

The surgical procedure for ovarian cystectomy has been published previously and the technique is considered standard, however the learning curve is long.[16] The preferred procedure is to incise the thin ovarian tissue surrounding the cyst and then, using opposing graspers, strip the cyst wall from the adjacent ovarian tissue, resulting in complete enucleation, known as the "stripping technique." Dissection of difficult-to-peel areas may be performed sharply, bluntly, or with hydro-dissection. Hemostasis may be obtained using sutures or electrocautery, as despite mildly elevated FSH levels three months after cauterization, ovarian volume and antral follicle count return to normal values.[17] If there is concern for malignancy not appreciated preoperatively, frozen pathological analysis can clarify if intraoperative consultation to gynecologic oncology, if available, is necessary. Another point to consider is that adnexal masses may actually be associated with the fallopian tube as opposed to the ovary once directly visualized. Cystectomy is again the preferred surgical approach with ovarian conservation; the fallopian tube, if grossly distorted or involved with the mass, should be removed to prevent increased ectopic pregnancy risk in the future. Ovarian torsion, if encountered, may be untwisted, with cystectomy performed if a mass is present, and the ovary left in-situ regardless of the appearance; this procedure has been shown to be safe and effective since 1946.[11]

SUMMARY AND RECOMMENDATIONS

Currently, recommendations for management of adnexal masses in children and adolescents should be as conservative of ovarian tissue as possible to reduce the risk of premature menopause and infertility. Preoperative workup should include:

- Thorough history and physical exam
- Transabdominal and transvaginal pelvic ultrasonography, including Doppler of the ovarian arteries, maximum diameter, and mass characteristics
- Serum markers for alpha-fetoprotein (AFP), beta human chorionic gonadotropin (βHCG), and lactate dehydrogenase (LDH)

If surgery is indicated, criteria with a high negative

likely ratio for malignancy should be applied with negative results leading to minimally invasive ovarian conserving surgery:

- Maximum diameter less than 8 cm
- No solid components to the mass
- Negative serum tumor markers

Surgical management should include ovarian cystectomy *via* enucleation for symptomatic benign neoplastic adnexal masses, persistent asymptomatic benign masses, and de-torsion for ovarian torsion. If tumor markers have not obtained or have not resulted given an acute abdomen, it has been advocated to still proceed with ovarian cystectomy unless highly suspicious on imaging studies. Unless malignancy is definitive on frozen pathology (which is rare), ovarian cystectomy is the approach of choice; it is preferable to perform a second staging surgery once final pathology verifies the malignancy which is in contrast to what is recommended in older women. Management of malignant masses may be minimally invasive or open, however consultation and referral to Gynecologic Oncology is recommended for oophorectomy and staging as appropriate.

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CONFLICTS OF INTEREST

Authors report no direct conflicts of interest for this manuscript.

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SURGICAL RESEARCH

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Case report

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Acute Digital Ischemia In a 30-Year Old Man: A Case Report

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ABSTRACT

Objective: To report a rare case of acute digital ischemia at a young man.
Methods: A 30-year old man presented with painful bluish discoloration of the toes and palpable pedal pulses.
Results: Physical evaluation and urgent angiography revealed a severe stenosis of the right common iliac artery. Treatment started with a low molecular weight heparin for fifteen days and completed with a bilateral common iliac artery angioplasty after two months.
Conclusion: Blue toe syndrome is considered a relatively frequent manifestation of limb ischemia, especially in elderly patients. Treatment is based on surgical or percutaneous elimination of the source of embolisation and restoration of arterial perfusion. In this case report, we present an unusual case of blue toe syndrome caused by a severe common iliac artery stenosis at a 30-year-old male patient. Blue toe syndrome is a rare manifestation of peripheral arterial disease at younger patients, but physicians should be aware of this in order to include it in the differential diagnosis of acute lower limb ischemia.

KEYWORDS: Blue toe syndrome; Occlusion of small vessels; Emboli; Thrombi; Digital cyanosis; Angioplasty.

INTRODUCTION

Blue toe syndrome, described by Karmody in 1976[1] was the most common clinical manifestation of tissue ischemia, caused by small vessels occlusion, resulting to limb loss or even death.[2] The main symptom was a spontaneous onset of a painful bluish discoloration of the toes, usually in elderly patients, without vasospasm and with skin lesions related to the occluded artery. Differential diagnosis includes Raynaud's syndrome, a common cause of digital discoloration in young patients, usually, due to vasospasm disorders or rheumatological disorders. The most common causes of blue toe syndrome are aneurysms, atherosclerotic disease and microemboli due to acquired hypercoagulative disorders. Keen et al, reported that 85% of the emboli arises from aorto/iliac occlusive or aneurismal disease.[3] Aneurysms located on the aorto- iliac and/or femoro- popliteal arterial system and the ulcerated atherosclerotic plaque can typically lead to embolisation, which manifests spontaneously.[4] Episodes of microembolisation can appear on elderly after vascular or endovascular surgical procedures regardless being covered by anticoagulation. The blue toe syndrome can be misdiagnosed on initial presentation, due to the often palpable pedal pulses which can mislead the physician to a non-vascular pathology diagnosis. Therefore, diagnosis can be most frequently confirmed by muscle and/or skin biopsy and fundoscopic examination which identifies the cholesterol crystals. Although surgery is the appropriate treatment for patients with aneurysms, for all the other causes of blue toe syndrome, surgery is rarely indicated because the origin of the emboli is not certain. Mild forms of the syndrome can subside without consequences and in some

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cases endovascular procedures (angioplasty with or without stenting) can eliminate the emboli source and substitute the need for reconstructive surgery.[5] Herein, we present a case of blue toe syndrome, which occurred in a young male.

CASE PRESENTATION

A 30-year-old Caucasian male presented at the emergency department of our hospital, with cyanosis and acute pain on the second, third and fourth toe of his right foot (Figure 1a). The patient was a heavy smoker and had untreated hypercholesterolemia, due to family history.

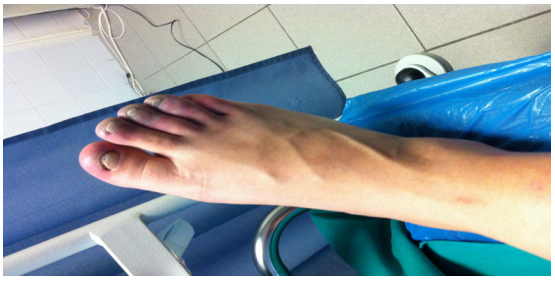

Figure 1a: Bluish discoloration of the toes.

Physical examination revealed a normotensive, obese male with fixed toe cyanosis of the right foot and palpable pedal pulses, but with an insidiously weak right femoral pulse. The laboratory testing revealed normal white cell count (9.897 k/ml with an eosinophil count of 1.8%) and normal serum creatinine (0.8 mg/dl).

Urgent angiography of the aorta and the arteries of the lower limbs revealed a severe stenosis of the right common iliac artery and a mild stenosis of the left one (Figure 1b). Aspirin and statin were prescribed and the patient was treated as an outpatient with a low molecular weight heparin (Tinzaparin sodium 14.000 [iU]/0.7 mL) for fifteen days. After two months the patient was readmitted for scheduled bilateral common iliac angioplasty and was discharged two days afterwards.

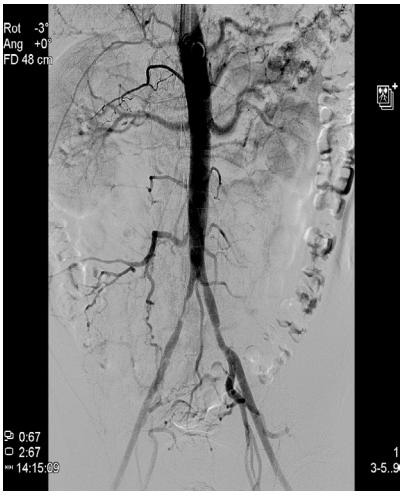

Figure 1b: Angiography revealed severe stenosis of the right common iliac artery.

DISCUSSION

Although blue toe syndrome most commonly appears in elderly men after invasive vascular procedures and is associated with cholesterol crystal embolisation, our patient was a young male with no history of invasive vascular procedure or symptoms of peripheral arterial occlusive disease. Prior to the cyanosis of the digits, pain was the main symptom. We ruled out all possible causes and concluded to the extensive iliac atherosclerotic stenosis, regardless the patient's age. In such cases, it is mandatory to eliminate the risk factors of atherosclerosis and control the extension of tissue lesion, even though the treatment of pain is often disproportionate. The administration of aspirin[6] can help temporarily restore the circulation and relief the pain, but anticoagulation should be discontinued.[7] Antiplatelet therapy is the cornerstone of conservative medical treatment for blue toe syndrome and in this case, after the diagnosis was made, we started treatment with low weight heparin for fifteen days. The aim of this treatment was to eliminate the source of emboli and the need for surgical operation as the patient was at a young age.

In conclusion, the most commonly responsible arterial part for symptomatic embolisation is the aorto-iliac axis. The manifestation of digital cyanosis can range from an isolated cyanotic toe to a multiorgan system disease. Due to the palpable distal pulses, progression to gangrene is unusual, while treatment should include elimination of the embolisation source by conservative or invasive means. In order to determine the origin of emboli it is highly useful to order a non-invasive vascular testing and imaging, echocardiography and angiography of aorta and peripheral arteries. Surgery remains the indicative treatment for patients with aneurysms, but antiplatelet therapy is one of the most effective treatments in mild cases of the syndrome. Our case is a good example of the manifestation of the blue toe syndrome in a 30-year-old young male.

DECLARATION OF CONFLICTING INTERESTS

The authors report no financial relationships or conflicts of interest regarding the content here in.

ETHICAL APPROVAL

Our institution does not require ethical approval for reporting individual cases or case series

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INFORMED CONSENT

Verbal informed consent was obtained from the patient for her anonymized information to be published in this article.

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