Review Article

Medical complications of liver transplantation

Julie H. Zhu[1], Trana Hussaini[2], Siegfried R. Erb[1], Vladimir Marquez[1], Eric M. Yoshida[1]

[1]Division of Gastroenterology, University of British Columbia, Vancouver, Canada; [2]Faculty of Pharmaceutical Sciences, University of British Columbia and the Liver Transplant Program of the Vancouver General Hospital, Vancouver, Canada

Contributions: (I) Conception and design: T Hussaini, EM Yoshida, JH Zhu; (II) Administrative support: EM Yoshida; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: JH Zhu; (V) Data analysis and interpretation: JH Zhu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Eric M. Yoshida, MD, MHSc, FRCP(C). Vancouver General Hospital, Diamond Health Care Centre, 5153-2775 Laurel Street, Vancouver, BC, V5Z 1M9, Canada. Email: eric.yoshida@vch.ca.

Abstract: Orthotopic liver transplantation has become the standard of care for adult patients with end-stage liver diseases. Knowledge in post-transplant medical complications has grown considerably in the last few decades. Graft rejection occurs in both early and late settings, and its diagnosis is confirmed and severity graded by a core needle liver biopsy. Acute rejections should be treated appropriately to avoid graft loss whereas chronic ductopenic rejection carries a poor prognosis without re-transplantation. The causes of acute kidney injuries are different from that of the chronic renal disease in post-transplant setting. With increasing prevalence of non-alcoholic fatty liver disease (NAFLD) and older transplant recipients, *de novo* diabetes and metabolic bone disease are becoming more recognized in the post-transplant era. *De novo* malignancy, post-transplant lymphoproliferative disorder, although less common, signals significant mortality in this population. The outcomes of graft rejection, renal dysfunction, diabetes, bone disease and *de novo* malignancy are dependent on timely recognition, alterations of the immunosuppression regimen, and occasionally liver re-transplantation in the setting of irreversible graft rejection and kidney transplantation in end-stage renal disease (ESRD). There is still significant mortality and morbidity associated with these medical complications despite our medical advances.

Keywords: Liver transplantation; acute and chronic graft rejection; renal dysfunction; *de novo* malignancy; medical complications

Received: 10 December 2017; Accepted: 02 January 2018; Published: 12 January 2018.

doi: 10.21037/amj.2018.01.03

View this article at: http://dx.doi.org/10.21037/amj.2018.01.03

Introduction

In the 21st century, more than 20,000 orthotopic liver transplantations are performed around the world each year, and about 400 of them are performed in Canada annually (1). With the availability of various immunosuppression medications, major medical and surgical advances, the survival rates have improved to 85–95% at 1-year and 75% at 5-year from that of 23.7% at 1-year from Cambridge/King's College Series of 93 Cases between 1968–1980 (2,3). In the first trials of orthotopic liver transplantation, patients died from haemorrhage, hepatic failure, pulmonary emboli and sepsis that took place in the first 23 days post-transplant (3). In the pre-cyclosporine era, main causes of deaths were attributed to liver failure and sepsis (3). In the cyclosporine era, causes of deaths were sepsis, operative, hepatic artery thrombosis, acute and chronic rejections occurring 1–20 months post-transplant (3). With the introduction of effective direct acting antiviral agents against hepatitis C, the number of referrals for end-stage HCV have been decreasing but with an increasing proportion with non-alcoholic fatty liver disease (NAFLD) to maintain a tragic status quo. Between 2002 and 2014, the average age of adult transplant registrants changed from 51.2 to 55.7 years, corresponding to an increase by 22% in age ≥60 from 19% to 41% (4). With an increasing number of liver transplants, the fact that liver recipients are living longer post-transplant,

recipients are older at transplant and an increasing prevalence of NAFLD, there is a gradual evolution of post-transplant medical complications, which is becoming more conspicuous. The time division of the early versus late medical complications is rather arbitrary, however it is generally divided into the first 3–6 months, 6–12 months and after 1-year post-transplant. This paper reviews some of the common early complications in the first few months: acute graft rejection and acute kidney injuries, as well as the late complications such as chronic graft rejection, chronic kidney disease (CKD) and metabolic bone disease. *De novo* malignancy and new-onset diabetes can occur both early and late post-transplant.

Post-transplant allograft rejection

Hepatic allograft rejection is an inflammatory pathologic condition elicited by a genetic disparity between the donor and recipient. Graft rejection can be from T-cell mediated or antibody-mediated processes (5). The process predominantly targets interlobular bile ducts and vascular endothelia, including portal veins and hepatic venules, and occasionally the hepatic artery and its branches (6). Most acute graft rejection happens in the first 3 months post-transplant but can occur at any time (7). Late acute rejection (LAR) is sometimes defined as biopsy-proven acute rejection occurring more than 180 days post-transplant, although the temporal definition is arbitrary (7). Acute rejection can lead to chronic rejection and graft loss (8).

Previously, acute rejection was reported to occur in 45–75% patients in the cyclosporine era of transplantation (7,9,10). In the tacrolimus/mycophenolate mofetil era, the combination of tacrolimus, mycophenolate mofetil, tapering corticosteroids, with or without an IL2 receptor antagonist was associated with an incidence of acute rejection of 23–28% in a randomized clinical trial (11). Even more recently, biopsy-proven acute rejection was found to occur in 15–27% of a cohort of 45,432 liver recipients (12). LAR has an incidence of 7–24% among acute rejections (8,13). The incidence of acute and chronic antibody-mediated rejection (AMR) is difficult to capture accurately as the diagnosis is still challenging to confirm in liver transplantation (5). Risk factors leading to acute rejection are broad, ranging from allograft-specific, patient-specific, immunosuppression-medication-specific factors, to transplantation for specific-disease-type factors. The reported allograft risk factors were donor/recipient HLA-DR mismatch, cold-ischemic time greater than 15 hours and donor age older than 50 years which independently associated with time to rejection (9). In contrast, recipient age inversely correlated with the likelihood of rejection (9,12). Patient noncompliance leads to an overall lower degree of immunosuppression, and is one of the leading causes of allograft rejection (8). Similarly, low trough cyclosporine levels and withdrawal of maintenance steroids predispose to the risk of LAR (13). Types of immune-suppressants also play a pivotal role in the occurrence of rejections. It has been reported that cyclosporine use and not tacrolimus, and combined immunosuppression drugs that do not including mycophenolate mofetil, are associated with LAR episodes (7). Transplantations for specific liver disease also seem to negatively impact allograft outcome. Primary biliary cholangitis (PBC) and HCV were associated with higher incidence of acute rejection observed in a cohort from 2003–2014 (12); statistics seen in HCV may change with the availability of direct-acting anti-viral agents for post-transplant untreated HCV patients in many parts of the world. Autoimmune hepatitis (AIH), non-metabolic and non-retransplanted patients also have more LAR episodes (7). The likelihood of chronic rejection increases with the occurrence of LAR.

To diagnose allograft rejections, the gold standard is core needle liver biopsy. In acute rejection, core needle biopsy demonstrates 2 or more features of: (I) mononuclear portal inflammation, frequently eosinophils, as well as activated lymphocytes and neutrophils; (II) bile duct inflammation and damage; (III) sub-endothelial inflammation of portal veins or terminal hepatic venules (i.e., endotheliitis) (6). The pathology of LAR is quite similar to that of the acute rejection as opposed to chronic rejection. The differences are fewer blastic lymphocytes, greater interface activity, less venous sub-endothelial inflammation, and higher lobular activity (6). Chronic rejection, also known as ductopenic rejection, on histology is characterized by focal ongoing lymphocytic bile duct damage, bile duct senescence, atrophy, and eventual bile duct loss (14). Nevertheless, the biopsy changes of acute and chronic rejection can sometimes be difficult to distinguish from non-rejection-related causes; thus other etiological mimickers should be screened and ruled out, such as biliary strictures, hepatic artery surgical complications, adverse drug reactions, cytomegalovirus (CMV), HBV, HCV, recurrent PBC and post-transplant AIH (14).

The clinical findings of early mild acute rejection are often lacking or too subtle to be reliable. In late or severe cases, one may find presentations of fever, allograft

tenderness, swelling, cyanosis and sometimes ascites (14). Laboratory tests are neither sensitive nor specific, however typically showcase liver enzyme de-arrangements in cholestatic or mixed patterns, with elevations of -glutamyl transpeptidase and alkaline phosphatase (1,5). Liver enzyme profile of chronic rejection is that of cholestasis, often indistinguishable from laboratory abnormalities produced from biliary tract obstruction/strictures, HBV, HCV, or recurrent AIH (14). Grading of acute allograft rejection is useful to determine the severity of rejection, and in turn can prognosticate graft outcomes (9,15). International grading system of severity of acute rejection uses Rejection Activity Index (RAI) in accordance to the Banff Schema (6). Three specific features, portal inflammation, bile duct damage/inflammation and venular inflammation are individually evaluated and assigned a score between 0 to 3 (mild, moderate and severe). The three components are added to arrive the final RAI (6).

In the last few years, acute and chronic AMR has gained more attention in liver transplantation (16). Mediated by ABO-incompatibility, donor-specific antibodies against ABO antigens or HLA class 1 and 2 antigens expressed on endothelial cells, the process instigates attraction and margination of leukocytes, formation of fibrin microthrombi, and fibrosis leading to shunting of blood flow, hypoxia and impaired function (5). The diagnosis is supported by liver biopsy features, serum DSA testing, C4d tissue staining, and exclusion of other causes (5).

Acute rejection can progress rapidly without treatment however is usually reversed by treatment. Up to 70% of acute rejections are considered mild (RAI ≤4) on histology and are not of clinical significance (15). Mild rejections may not need additional immunosuppressive treatment and may not lead to allograft impairment (6). Earlier studies examining outcomes found no significant increase in patient mortality from acute rejections, apart from higher healthcare costs secondary to longer hospital stays (10). Graft failure was considered a rarity, affecting 1% of patients in a study conducted in 2002 (15). About 17% of acute rejections are graded moderate to severe on biopsy in the tacrolimus era (15). Moderate-severe rejection was associated with a likelihood of perivenular fibrosis (15), with severe rejection predicting shorter time to re-transplantation and death (9). These findings stood in contrast to the Adult-to-Adult Living Donor Liver Transplantation Cohort Study published in 2017. Analysis of a large cohort (2003 to 2014) found liver related mortality from primary graft failure was uniformly 4–8 times higher in those diagnosed with at least one episode of acute rejection, irrespective of the severity of rejection (12). In the past, many centers followed protocols to treat moderate-to-severe acute rejections (RAI ≥5) with additional immunosuppressive therapy to avoid negative consequences. No specific therapeutic recommendation can be made in mild acute rejection, although after optimization of existent immunosuppression regimen, some centers recommend performing a follow-up liver biopsy to confirm its resolution whereas others will give additional treatment. The reported outcome from acute rejection is likely to shift in light of the newer cumulative data from recent years.

The majority of acute rejections, including the moderate-to-severe, are treated with and responsive to single or multiple courses of high-dose steroids (7), while 5–10% will be steroid resistant (17). Variations in the duration of initial steroid treatment are often dictated by center-specific preference. A small-randomized trial comparing 1-day intravenous steroid followed by 6-day oral taper with that of 3-day intravenous steroid regimen reported better effectiveness and side-effect profile of the former, a generalization that may require further validation (17). In the case of steroid resistance, the therapeutic options are OKT3, anti-thymocyte globulin (ATG) and sometimes anti-IL2 receptor antibodies (basiliximab or daclizumab) (13,18,19). The reported success rate of rabbit ATG in steroid resistant acute rejection (SRAR) is 77–100% (18). The use of OKT3 is associated with complete reversal of hepatic rejection in 45% of patients with SRAR, and partial reversal in 38% (18). LAR can lead to increased graft loss and morbidity. Persistent acute rejection can result in allograft failure from chronic rejection. Chronic rejection usually responds poorly to rescue therapy (19) and re-transplantation is the only viable solution. In AMR, prevention is key. There are currently no prospective studies in the treatment of liver transplant patients diagnosed with moderate-to severe acute AMR. The small number of published case reports documented variable success rates using plasmapheresis, IVIG, rituximab, and proteasome inhibitors (16).

Post-transplant renal dysfunction

Renal dysfunction can be acute or chronic post-transplant. The creatinine-based GFR estimation in patients with cirrhosis and post-transplant is adopted from non-liver related literatures; its applicability and accuracy in the post-transplant setting have been questioned. A proposal by a group of international hepatologists outlined

necessary revisions to the definitions of AKI and CKD in patients with cirrhosis (20). Similarly, currently there is no consensus definition of AKI or CKD specific to the liver-transplant settings (21). Of the papers reviewed hitherto, CKD is defined, by the authors, as an onset of GFR <29 mL/minute/1.73 m^2 or the development of end-stage renal disease (ESRD) (22).

One, 3- and 5-year accumulative incidence of post-transplant CKD is reportedly 8%, 14% and 18%, higher than that of heart and lung transplant and second only to intestine transplant (22). Using variable AKI definitions, post-transplant AKI incidence ranges from 17% to 94% (23-25).

In post-transplant renal dysfunction, the leading culprits are found at time of transplant and post-transplant. At time of transplant are ATN, residual pre-transplant renal dysfunction and calcineurin inhibitor-related acute renal dysfunction (i.e., nephrotoxicity from cyclosporine or tacrolimus) (21). In the post-transplant period, post-transplant DM, hypertension, CNI-related acute or chronic renal dysfunction and ATN are known contributors to declining GFR (21). Specific patient demographics were identified as risk factors in CKD post-transplant: older age, female gender, African American background, while important past medical history of pre-transplantation HCV, hypertension, BMI ≥35, DM were additional factors (22,26). Postoperative acute kidney failure is associated with CKD, with a relative risk of 2.13, as well as an association with mortality, suggesting the degree of AKI may determine long-term outcome (22,24,25). Transplantation for cholestatic liver disease, low sodium <134 mEq/L, and status-1 listing were negative predictors of post-transplant ESRD (26).

In late-onset AKI, the risk factors are bacterial infection and the need for reoperation (21). The etiologies of CKD are different from those of AKI. In CKD, the major factors are calcineurin inhibitor induced nephrotoxicity (48%), hypertensive vascular changes (44%), membranoproliferative glomerulonephritis (17%), IgA nephropathy (9%), diabetic nephropathy and ATN (27). Calcineurin inhibitors are causes of acute dose-dependent nephrotoxicity as well as chronic non-dose dependent nephrotoxicity (28). Calcineurin inhibitors cause vasoconstrictions of afferent and efferent arterioles by mechanisms of increased release of endothelin-1, decreased production of nitric acid and increased expression of TGF-beta (28,29).

The risk of renal dysfunction can be minimized with careful titration of the tacrolimus dose to the tacrolimus trough level. This is especially important in the immediate post-transplant period and the use of a low dose delayed tacrolimus regimen with mycophenolate mofetil and an IL2 receptor antagonist, has clearly been showed to be associated with an improved GFR during this early time period (11). Similar kidney-sparing strategy using calcineurin free regimen was utilized by another randomization study (30). Sirolimus was used as a reasonable alternative in 14 patients developing tacrolimus nephrotoxicity in the immediate post-transplant stage and measures of acute rejection were equivalent at 90 days (31). CNI dose-reduction has been thought futile once CKD develops. In a randomized study comprising 27 patients with CKD, introduction of mycophenolate mofetil and 50% CNI dose reduction at minimal created significant improvement in measures of creatinine clearance at one year with comparable graft outcomes. This was in comparison with another 29 patients from the same study, where CNI dose reduction at 25% had negligible effect on GFR (32). CKD post-transplant significantly increases the risk of death with a relative risk of 4.55 (22). Patients who eventually develop end stage renal disease (ESRD) do better with a renal transplant than those on dialysis only. Treatment of ESRD by renal transplantation is associated with reduced 5-year risks of death than with dialysis (22).

Post-transplant *de novo* diabetes mellitus

Diabetes mellitus is often a lead-in diagnosis for liver transplantation especially in NAFLD, and those without a history can develop *de novo* post-transplant diabetes mellitus (PTDM). Specific diagnostic criteria of DM are outlined in the American Diabetes Association and the World Health Organization (33).

The prevalence of *de novo* PTDM was reportedly 27%, 9% and 7% at 1, 2 and 3 years post-transplant, respectively (34). The decrease in prevalence over time is likely related to reducing steroid use, which is a major risk factor in *de novo* PTDM. A Canadian retrospective review of 177 liver-transplant patients documented 17% *de novo* PTDM and 24.3% PTDM (35). Variations in the incidence and prevalence of *de novo* PTDM and PTDM may be explained in part by different diagnostic criteria used in post liver-transplant literatures.

Aside from the effects of antirejection drugs, notable patient-specific risk factors for developing *de novo* PTDM and PTDM are older age, male gender, obesity, African American background, family history of diabetes, transplantations

for HCV or alcohol cirrhosis (35,36). In a cohort of 17,000 HCV patients, the prevalence of *de novo* PTDM was 35.2% versus 18.9% in HBV comparator arm, and HCV was an independent predictor of *de novo* PTDM with adjusted hazard ratio (HR) 1.55 (37). The pathogenesis of HCV-associated DM is conjectural. Possible physiological mechanisms are decreased insulin secretion, HCV-directed damage on pancreatic beta-islet cells, insulin resistance from NAFLD, and increased iron stores (38). Oral and IV corticosteroid are well-known iatrogenic causes of DM in general and the risk is duration dependent, although not strictly dose-dependent (39). Similarly, CNI is associated with the development of *de novo* PTDM. Tacrolimus is associated with greater risk than cyclosporine with a relative risk of 1.38 reported by a systematic review of 16 randomized trials; 33% of the tacrolimus cohort developed PTDM while it occurred in 19% of the cyclosporine cohort at 6 months post liver transplant (40,41).

Screening of *de novo* PTDM should be conducted in all post-transplant patients regardless of the presence of specific risk factors mentioned above and/or symptoms of hyperglycemia. Fasting plasma glucose monitoring at regular intervals in all recipients post-transplant as well as pre-lunch, dinner and evening glucometer checks while in the early post-operative period are mandatory. In PTDM, glycosylated haemoglobin level at 3-monthly interval is recommended and levels above 6.5% should be medically intervened (42). All PTDM patients should be assessed annually for diabetic complications. Management of PTDM should consist of assessment by an endocrinologist, dietary modifications, minimization of steroid exposure when possible,, single and combination oral anti-hyperglycemic agents, and insulin use (42).

De novo PTDM and PTDM likely has more profound effect on long-term than short-term transplant outcomes. A Canadian study found no difference in mortality or graft survival between groups with or without PTDM following the first one year post-transplant (35). In contrast, another study reported worse prognosis associated with PTDM compared to those without, in measures of rejection episodes at 1 year and mortality at 2 years (34). A U.S. study reported worse long-term outcomes over 8–10 years in rates of infection, graft failure from chronic rejection and late hepatic artery thrombosis, significant in individuals with persistent PTDM (duration >6 months), a trend not seen in transitory PTDM (duration 1–6 months) (43). Supported by another study there were higher long-term rates of infection and mortality in PTDM group (44).

Post-transplant metabolic bone disease

The spectrum of metabolic bone disease, osteopenia, osteoporosis and bone fractures, is common in post liver-transplant recipients. The diagnosis of osteopenia and osteoporosis requires a bone mineral density (BMD) test such as dual-energy X-ray absorptiometry (DEXA). About 38% patients develop vertebral collapse post-transplant (45) as a result of osteopenia which peaks in the 2 years post-transplant (46). In another study, vertebral and non-vertebral fractures were diagnosed in 14% and 7% at 1 year respectively and 21% vertebral fractures occurred within the first 2 years post-transplant (46). The greatest incidence was seen in patients transplanted for cholestatic liver diseases. About 43% and 30% liver recipients for PBC and PSC sustained fractures in the first year, respectively (47,48).

Patient-specific risk factors of post-transplant metabolic bone diseases are female gender, older age, post menopause and a pre-transplant history of vertebral fracture (46,49). Pre-transplant BMD t score when above –2.5 standard deviation (SD) did not reliably predict post-transplant fractures however t score below –2.5 SD predicted vertebral fracture risk (46). Transplantation for cholestatic liver disease (PBC, PSC), post-transplant cholestasis, prolonged bed-rest and immobility are other predisposing factors of metabolic bone disease (45,47,48).

Causes for metabolic bone disease in post liver transplant population are multifactorial. Osteopenia and osteoporosis are prevalent in 10–40% of patients with end-stage liver diseases pre-transplant, and these conditions likely persist in the post-transplant period (48). Hypogonadism is also likely to persist post-transplant. Additionally, there was increased bone turnover rate at 3 months post-transplant as measured by histomorphometric analysis of bone remodelling in 21 patients, a process that can weaken bone strength (50). In a study involving women transplanted for PBC, lumbar BMD was significantly decreased at 3 months post-transplant, however by 12 months BMD returned to pre-transplant level and by 24 months was 5% above it (51). Corticosteroid use in the post-transplant period is a major culprit to trabecular bone loss, by a myriad of mechanisms, notably accelerated bone resorption and osteoclast activity (52). No dose-dependent relationship was found between cyclosporine or tacrolimus with risk of fractures (46). They may be less likely culprits for post-transplant bone disease, although cyclosporine and tacrolimus cause high-turnover osteopenia in animal studies (53).

All reversible factors for bone loss should be assessed and

treated in a timely fashion. This includes baseline evaluation of serum calcium, vitamin D, parathyroid hormone level, and gonadal function at 4–6 months post-transplant. Steroids use should be minimized when possible. Persistent hypogonadism should be considered for hormonal replacement therapy. Bone density generally improves after 4–6 months post liver transplant from the process of increased bone formation. A study found ongoing bone recovery happened in some patients up to 4 years post-transplant and some required 85 months to return to pre-transplant baseline (54).

Post-transplant *de novo* malignancy

Skin, haematological, oropharyngeal, lung and colon cancers are more frequently encountered in the post-transplant population (55). Post-transplant lymphoproliferative disorder (56) is a spectrum of lymphoid or plasmacytic proliferations associated with solid organ transplant or allogeneic hematopoietic cell transplant with the use of potent immunosuppressive drugs after solid-organ transplantation (56).

The overall incidence of *de novo* cancer post-transplant is about 2.5 times of the general population according to a Canadian study of 2,034 patients, and the risk is most pronounced in the first year post-transplant (57). The combined incidence in post-transplant population can be as high as 21.4% from long-term follow-up data (58), with variable reports of lower range about 2–15% depending on the length of follow-up (59). The reported 1, 5, 10 and 20 years accumulative incidence rates were 3%, 5%, 13% and 16%, respectively (60). Looking at a composition of *de novo* malignancy, 54.2% were skin-cancer related, 10.7% were haematological, and 35% were from solid organs (58). Similar composition was seen in a Finnish cohort of 540 patients, where the most common cancers arose from non-melanoma and non-Hodgkin lymphoma (60). PTLD occurs in 2.3–3.3% of post liver transplant recipients at a median time of 6–10 months, with a reported incidence of 2.44 per 1,000 person-years (61-64). Incidence of PTLD is 3 times higher and median onset shorter in children (65). The incidences of breast, ovarian and prostate cancers were reported to be not increased in the post-transplant population compared to the general population (57).

Pertaining to patient demographics, male gender, younger age (below versus above 40 years) is associated with an overall higher standard incidence ratio (SIR) of *de novo* malignancy while other studies found cancer risk steadily increasing with age (57,60). Age has variable impact on the types of malignancy. Non-Hodgkin lymphoma is more likely to affect the young while skin and colon cancer is more common in older ages (55,60). A systematic review of a large cohort of patients identified specific risk factors associating with various types of *de novo* malignancy (66). Age >40 years, male, red hair, brown eyes, sun exposure, transplantation for alcohol liver disease, cyclosporine use are risk factors in the development of skin cancer. It has been reported that specific liver diseases at transplantation predispose to solid malignancy post-transplant, amongst them, PSC and alcoholic liver disease were identified, with HRs 2.5 and 2.1, respectively (58). Transplantation for alcohol liver disease was associated with increased oropharyngeal and lung cancer at 5 years compared to their non-alcohol counterpart (67). In addition, history of pre-transplant smoking was associated with oropharyngeal cancer post-transplant (68). Transplantation for PSC and history of inflammatory bowel disease are associated with *de novo* colorectal cancer (55,66,69). Non-Hodgkin's lymphoma in post-transplant population is associated with younger age, male gender and the immediate post-transplant period (70).

Risk factors in developing PTLD are Epstein-Barr virus (EBV) infection, age >50, transplantation for HCV or alcohol cirrhosis, use of anti-lymphocyte antibody, and rejection therapy with high-dose steroids (61,66). The main risk factor of PTLD is infection or reactivation with EBV, particularly in EBV sero-negative recipient with EBV sero-positive donor (61). About 70% of adult PTLD tumors are EBV positive, while in children 98% (65). The transformation of B-cell associated lymphoproliferative disorder in EBV-positive immunosuppressed patients is mediated by EBV latent membrane protein 1 signal transduction to intracellular growth factors (71). EBV LMP1 is expressed in post-transplant lymphoproliferative tumors, and through cytoplasmic TNF receptor-associated factors (TRAFs) it promotes B cell growth (71). HCV has been shown to enhance B cell proliferation in non-transplant patients and in liver transplant population, can synergistically trigger EBV oncogenicity (61). A causative role of HCV is established in mixed type II cryoglobulinemia, which is now considered a type of B-cell lymphoproliferative disorder. EBV negative PTLD may be a distinct entity and is becoming more recognized (56). While some studies find younger age, male gender to be risk factors in PTLD, the common denominator is likely the overall degree of immunosuppression (60,63).

The presentation of PTLD may be non-specific or involvement of single or multiple sites. Lymph node involvement occurs in 35% cases, followed by gastrointestinal involvement in 25%, liver and spleen in 16% cases, as well as pulmonary (11%) and CNS (4%) (65). A tissue diagnosis and computer tomography to assess disease extent are highly recommended (72). WHO classification subdivides PTLD into (I) early lesions, (II) polymorphic PTLD, (III) monomorphic PTLD (which includes B and T cell NHLs), and 4) Classical Hodgkin lymphoma (73).

Stepwise approach to PTLD treatment should begin with the reduction or complete withdrawal of immunosuppression, followed by various chemotherapies, radiation therapy or surgery (65,74,75). Reduction of immunosuppression alone results in tumor regression in up to 50% cases in retrospective studies (63). However regression rate from a prospective study is significantly lower, with partial remission rates as low as 12.5% and no complete remission with immunosuppression reduction alone (74). Antiviral therapy with acyclovir or valganciclovir is controversial with various degrees of success (64). In CD20-positive B-cell PTLD, rituximab adjunct therapy was tried with 44.2% response rate at one year in a prospective phase 2 study (76). Rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) sequential therapy instead of R-CHOP concomitant may minimize the cytotoxic effect of CHOP (56). Finally, re-transplantation, although tried successfully in children, remains a controversial option for adults who have lost graft function due to having to reduce immunosuppression as a consequence of PTLD (63).

De novo malignancy is one of the leading causes of deaths in liver-transplant recipients. After diagnosis of haematological or solid malignancy, risks of death were 44% and 38% at 1 year, 57.6% and 53.1% at 5 years respectively (58). In oropharyngeal cancer, 5-year survival rate was 41.5% (68). Patients with *de novo* cancer have significantly lower 10-year survival than those without at 39% versus 75% (77). PTLD is associated with 15-year survival of 39–45% (61,65). Tacrolimus versus cyclosporine use, single versus multi-site PTLD are associated with better survival at 12 years (65). *De novo* malignancy raises needs for more medical attention in this population, particular in PTLD prevention, detection and treatment. The roles of antiviral prophylaxis, monitoring of EBV viral load and preemptive antiviral therapy should be further studied and clarified. One may see reduction of PTLD risk by implementing changes in immunosuppressive therapy, such as caution with ATG in patients transplanted for HCV-related cirrhosis has been recommended (61).

In summary this review outlines the various aspects of post liver transplant medical complications that occur early and late. Early diagnosis, treatment and surveillance for these complications are essential to improve patient care and survival, as well as to maintain allograft longevity. Calcineurin-related renal dysfunction remains a problem in post liver transplant recipients, however various renal-sparing strategies yielded improved outcomes. A standardized approach to diagnosis, surveillance and management of PTDM and PTLD are likely beneficial.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *AME Medical Journal* for the series "Liver Transplantation". The article has undergone external peer review.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.01.03). The series "Liver Transplantation" was commissioned by the editorial office without any funding or sponsorship. Dr. Yoshida and Dr. Hussaini serve as Associate Editors-in-Chief of *AME Medical Journal* and the unpaid Guest Editors of the series. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Shimazono Y. The state of the international organ trade: a provisional picture based on integration of available information. Bull World Health Organ 2007;85:955-62.
2. Yoshida EM, Haque M, Scudamore CH. Adult live donor liver transplantation: routine, commonplace, standard care for end stage liver disease (we hope). Ann Hepatol 2010;9:89-90.
3. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982;2:614-36.
4. Su F, Yu L, Berry K, et al. Aging of Liver Transplant Registrants and Recipients: Trends and Impact on Waitlist Outcomes, Post-Transplantation Outcomes, and Transplant-Related Survival Benefit. Gastroenterology 2016;150:441-53.e6; quiz e16.
5. Lee M. Antibody-Mediated Rejection After Liver Transplant. Gastroenterol Clin North Am 2017;46:297-309.
6. Banff schema for grading liver allograft rejection: an international consensus document. Hepatology 1997;25:658-63.
7. Ramji A, Yoshida EM, Bain VG, et al. Late acute rejection after liver transplantation: the Western Canada experience. Liver Transpl 2002;8:945-51.
8. Mor E, Gonwa TA, Husberg BS, et al. Late-onset acute rejection in orthotopic liver transplantation--associated risk factors and outcome. Transplantation 1992;54:821-4.
9. Wiesner RH, Demetris AJ, Belle SH, et al. Acute hepatic allograft rejection: incidence, risk factors, and impact on outcome. Hepatology 1998;28:638-45.
10. Fisher LR, Henley KS, Lucey MR. Acute cellular rejection after liver transplantation: variability, morbidity, and mortality. Liver Transpl Surg 1995;1:10-5.
11. Yoshida EM, Marotta PJ, Greig PD, et al. Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen: a multicenter randomized clinical trial. Liver Transpl 2005;11:1064-72.
12. Levitsky J, Goldberg D, Smith AR, et al. Acute Rejection Increases Risk of Graft Failure and Death in Recent Liver Transplant Recipients. Clin Gastroenterol Hepatol 2017;15:584-93 e2.
13. Yoshida EM, Shackleton CR, Erb SR, et al. Late acute rejection occurring in liver allograft recipients. Can J Gastroenterol 1996;10:376-80.
14. Banff Working G, Demetris AJ, Adeyi O, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology 2006;44:489-501.
15. Demetris AJ, Ruppert K, Dvorchik I, et al. Real-time monitoring of acute liver-allograft rejection using the Banff schema. Transplantation 2002;74:1290-6.
16. Kim PT, Demetris AJ, O'Leary JG. Prevention and treatment of liver allograft antibody-mediated rejection and the role of the 'two-hit hypothesis'. Curr Opin Organ Transplant 2016;21:209-18.
17. Volpin R, Angeli P, Galioto A, et al. Comparison between two high-dose methylprednisolone schedules in the treatment of acute hepatic cellular rejection in liver transplant recipients: a controlled clinical trial. Liver Transpl 2002;8:527-34.
18. Lee JG, Lee J, Lee JJ, et al. Efficacy of rabbit anti-thymocyte globulin for steroid-resistant acute rejection after liver transplantation. Medicine (Baltimore) 2016;95:e3711.
19. Orr DW, Portmann BC, Knisely AS, et al. Anti-interleukin 2 receptor antibodies and mycophenolate mofetil for treatment of steroid-resistant rejection in adult liver transplantation. Transplant Proc 2005;37:4373-9.
20. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut 2011;60:702-9.
21. Weber ML, Ibrahim HN, Lake JR. Renal dysfunction in liver transplant recipients: evaluation of the critical issues. Liver Transpl 2012;18:1290-301.
22. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931-40.
23. McCauley J, Van Thiel DH, Starzl TE, et al. Acute and chronic renal failure in liver transplantation. Nephron 1990;55:121-8.
24. Bilbao I, Charco R, Balsells J, et al. Risk factors for acute renal failure requiring dialysis after liver transplantation. Clin Transplant 1998;12:123-9.
25. Barri YM, Sanchez EQ, Jennings LW, et al. Acute kidney injury following liver transplantation: definition and outcome. Liver Transpl 2009;15:475-83.
26. Sharma P, Goodrich NP, Schaubel DE, et al. Patient-specific prediction of ESRD after liver transplantation. J Am Soc Nephrol 2013;24:2045-52.
27. O'Riordan A, Dutt N, Cairns H, et al. Renal biopsy in liver transplant recipients. Nephrol Dial Transplant 2009;24:2276-82.

28. Olyaei AJ, de Mattos AM, Bennett WM. Nephrotoxicity of immunosuppressive drugs: new insight and preventive strategies. Curr Opin Crit Care 2001;7:384-9.
29. Lanese DM, Conger JD. Effects of endothelin receptor antagonist on cyclosporine-induced vasoconstriction in isolated rat renal arterioles. J Clin Invest 1993;91:2144-9.
30. Teperman L, Moonka D, Sebastian A, et al. Calcineurin inhibitor-free mycophenolate mofetil/sirolimus maintenance in liver transplantation: the randomized spare-the-nephron trial. Liver Transpl 2013;19:675-89.
31. Neff GW, Montalbano M, Slapak-Green G, et al. Sirolimus therapy in orthotopic liver transplant recipients with calcineurin inhibitor related chronic renal insufficiency. Transplant Proc 2003;35:3029-31.
32. Pageaux GP, Rostaing L, Calmus Y, et al. Mycophenolate mofetil in combination with reduction of calcineurin inhibitors for chronic renal dysfunction after liver transplantation. Liver Transpl 2006;12:1755-60.
33. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160-7.
34. Navasa M, Bustamante J, Marroni C, et al. Diabetes mellitus after liver transplantation: prevalence and predictive factors. J Hepatol 1996;25:64-71.
35. AlDosary AA, Ramji AS, Elliott TG, et al. Post-liver transplantation diabetes mellitus: an association with hepatitis C. Liver Transpl 2002;8:356-61.
36. Bigam DL, Pennington JJ, Carpentier A, et al. Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. Hepatology 2000;32:87-90.
37. Younossi Z, Stepanova M, Saab S, et al. The association of hepatitis C virus infection and post-liver transplant diabetes: data from 17 000 HCV-infected transplant recipients. Aliment Pharmacol Ther 2015;41:209-17.
38. Bahtiyar G, Shin JJ, Aytaman A, et al. Association of diabetes and hepatitis C infection: epidemiologic evidence and pathophysiologic insights. Curr Diab Rep 2004;4:194-8.
39. Marchetti P. New-onset diabetes after liver transplantation: from pathogenesis to management. Liver Transpl 2005;11:612-20.
40. Thoefner LB, Rostved AA, Pommergaard HC, et al. Risk factors for metabolic syndrome after liver transplantation: A systematic review and meta-analysis. Transplant Rev (Orlando) 2017.
41. Haddad EM, McAlister VC, Renouf E, et al. Cyclosporin versus tacrolimus for liver transplanted patients. Cochrane Database Syst Rev 2006;(4):CD005161.
42. Wilkinson A, Davidson J, Dotta F, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant 2005;19:291-8.
43. Moon JI, Barbeito R, Faradji RN, et al. Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: Long-term follow up. Transplantation 2006;82:1625-8.
44. Watt KD, Pedersen RA, Kremers WK, et al. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant 2010;10:1420-7.
45. Haagsma EB, Thijn CJ, Post JG, et al. Bone disease after orthotopic liver transplantation. J Hepatol 1988;6:94-100.
46. Goffin E, Devogelaer JP, Depresseux G, et al. Osteoporosis after organ transplantation. Lancet 2001;357:1623.
47. Crippin JS. Bone disease after liver transplantation. Liver Transpl 2001;7:S27-35.
48. Hay JE. Osteoporosis in liver diseases and after liver transplantation. J Hepatol 2003;38:856-65.
49. Burra P, De Martin E, Gitto S, et al. Influence of age and gender before and after liver transplantation. Liver Transpl 2013;19:122-34.
50. Vedi S, Greer S, Skingle SJ, et al. Mechanism of bone loss after liver transplantation: A histomorphometric analysis. J Bone Miner Res 1999;14:281-7.
51. Eastell R, Dickson ER, Hodgson SF, et al. Rates of vertebral bone loss before and after liver transplantation in women with primary biliary cirrhosis. Hepatology 1991;14:296-300.
52. Defranco DJ, Lian JB, Glowacki J. Differential effects of glucocorticoid on recruitment and activity of osteoclasts induced by normal and osteocalcin-deficient bone implanted in rats. Endocrinology 1992;131:114-21.
53. Epstein S. Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. J Bone Miner Res 1996;11:1-7.
54. Feller RB, McDonald JA, Sherbon KJ, et al. Evidence of continuing bone recovery at a mean of 7 years after liver transplantation. Liver Transpl Surg 1999;5:407-13.
55. Oo YH, Gunson BK, Lancashire RJ, et al. Incidence of cancers following orthotopic liver transplantation in a single center: comparison with national cancer incidence rates for England and Wales. Transplantation 2005;80:759-64.
56. Trappe R, Oertel S, Leblond V, et al. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2

PTLD-1 trial. Lancet Oncol 2012;13:196-206.
57. Jiang Y, Villeneuve PJ, Fenton SS, et al. Liver transplantation and subsequent risk of cancer: findings from a Canadian cohort study. Liver Transpl 2008;14:1588-97.
58. Watt KD, Pedersen RA, Kremers WK, et al. Long-term probability of and mortality from de novo malignancy after liver transplantation. Gastroenterology 2009;137:2010-7.
59. Chandok N, Watt KD. Burden of de novo malignancy in the liver transplant recipient. Liver Transpl 2012;18:1277-89.
60. Aberg F, Pukkala E, Hockerstedt K, et al. Risk of malignant neoplasms after liver transplantation: a population-based study. Liver Transpl 2008;14:1428-36.
61. Duvoux C, Pageaux GP, Vanlemmens C, et al. Risk factors for lymphoproliferative disorders after liver transplantation in adults: an analysis of 480 patients. Transplantation 2002;74:1103-9.
62. Hezode C, Duvoux C, Germanidis G, et al. Role of hepatitis C virus in lymphoproliferative disorders after liver transplantation. Hepatology 1999;30:775-8.
63. Johnson SR, Cherikh WS, Kauffman HM, et al. Retransplantation after post-transplant lymphoproliferative disorders: an OPTN/UNOS database analysis. Am J Transplant 2006;6:2743-9.
64. Dharnidharka VR. Comprehensive Review of Post-Organ Transplant Hematologic Cancers. Am J Transplant 2017.
65. Jain A, Nalesnik M, Reyes J, et al. Posttransplant lymphoproliferative disorders in liver transplantation: a 20-year experience. Ann Surg 2002;236:429-36; discussion 436-7.
66. Chak E, Saab S. Risk factors and incidence of de novo malignancy in liver transplant recipients: a systematic review. Liver Int 2010;30:1247-58.
67. Jain A, DiMartini A, Kashyap R, et al. Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. Transplantation 2000;70:1335-42.
68. Scheifele C, Reichart PA, Hippler-Benscheidt M, et al. Incidence of oral, pharyngeal, and laryngeal squamous cell carcinomas among 1515 patients after liver transplantation. Oral Oncol 2005;41:670-6.
69. Silva MA, Jambulingam PS, Mirza DF. Colorectal cancer after orthotopic liver transplantation. Crit Rev Oncol Hematol 2005;56:147-53.
70. Rathsman S, Tysk C, Eriksson S, et al. Elution of antitransglutaminase antibodies from duodenal biopsies: a novel approach in the diagnosis of celiac disease. APMIS 2012;120:666-74.
71. Liebowitz D. Epstein-Barr virus and a cellular signaling pathway in lymphomas from immunosuppressed patients. N Engl J Med 1998;338:1413-21.
72. Parker A, Bowles K, Bradley JA, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol 2010;149:675-92.
73. Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of hematological malignancies report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. Mod Pathol 2000;13:193-207.
74. Swinnen LJ, LeBlanc M, Grogan TM, et al. Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. Transplantation 2008;86:215-22.
75. Burra P, Rodriguez-Castro KI. Neoplastic disease after liver transplantation: Focus on de novo neoplasms. World J Gastroenterol 2015;21:8753-68.
76. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood 2006;107:3053-7.
77. Baccarani U, Adani GL, Serraino D, et al. De novo tumors are a major cause of late mortality after orthotopic liver transplantation. Transplant Proc 2009;41:1303-5.

doi: 10.21037/amj.2018.01.03
Cite this article as: Zhu JH, Hussaini T, Erb SR, Marquez V, Yoshida EM. Medical complications of liver transplantation. AME Med J 2018;3:11.

