KIDNEY TRANSPLANT RECIPIENT WITH KAPOSI SARCOMA

T.KASRADZE

Case 1

- 53 years old, male,
- Diagnosis: axial spondyloarthritis, Chronic tubulointerstitial nephritis, ESKD
- Hemodialysis since 2016
- KTx, transplanted in Belarus, Minsk in 2017
- Pretransplant Sensitization - Nonsensitized
- Induction immunosuppression -basiliximab
- Maintenance immunosuppression: Tacrolimus, MPA (720 mg b.i.d since transplant), methylprednisolone
- GFR- 71ml/min/1.73 m^2, Urinalysis N

- April 2021: red-purple coloured papules and macules of different size affecting the feet and lymphedema
- GFR- 73 ml/min/1.73 m^2, Urinalysis N
- IS: Tacrolimus (Blood level: 6ng/ml),
- MPA (720 mg b.i.d since transplant),
- methylprednisolone 2 mg,

Kaposi Sarcoma?

- **Biopsy of affected skin tissue:**
  Microscopy/immunohistochemistry: blood vessels proliferation with tight cleft like canals, oval and spindle-shaped endothelial type CD31 and HHV-8 positive cells. The existence of erythrocytes, extravasation, diapedesis and minimal perivascular lymphocytic infiltration of the dermis has to be noted. KI-67 is positive in 15% of the cells.
- Diagnosis: Kaposi Sarcoma
- CT Scan did not reveal visceral Involvement
- HIV - negative

MYFORTIC WAS REPLACED BY EVEROLIMUS (TARGET BLOOD CONCENTRATION 5-6 NG/ML), TACROLIMUS WAS REDUCED (TARGET TACROLIMUS LEVEL 4 NG/ML),

- Before reduction of the immunosuppressive regimen

- 1 year later after reduction of the immunosuppressive regimen

Case 2

- 43 years old, male, KTx, transplanted in Belarus, Minsk in 2019
- unknown primary underlying etiology of CKD
- Pretransplant Sensitization and induction immunosuppression - not available
- Maintenance immunosuppression: Tacrolimus, MMF (1000mg b.i.d since transplant), methylprednisolone

- 24.08.2020 unexplained increased of serum creatinine (1,6-1,8mg/dl) and low grade proteinuria (<3g/24h)

- Kidney Allograft biopsy: Chronic active antibody mediated rejection, Borderline (Suspicious) for acute TCMR, IFTA Grade 1

- g3, ptc2, C4d2, cg 1b, mm1, v0, cv1, i1, t1, ci1, ct1, ah 1
- Anti HLA class I positive, class II positive
- Treatment: Steroid pulse+ IVIG

- 12.04.2021 serum creatinine (2.0-2.3 mg/dl) and proteinuria (4.5 g/24h)

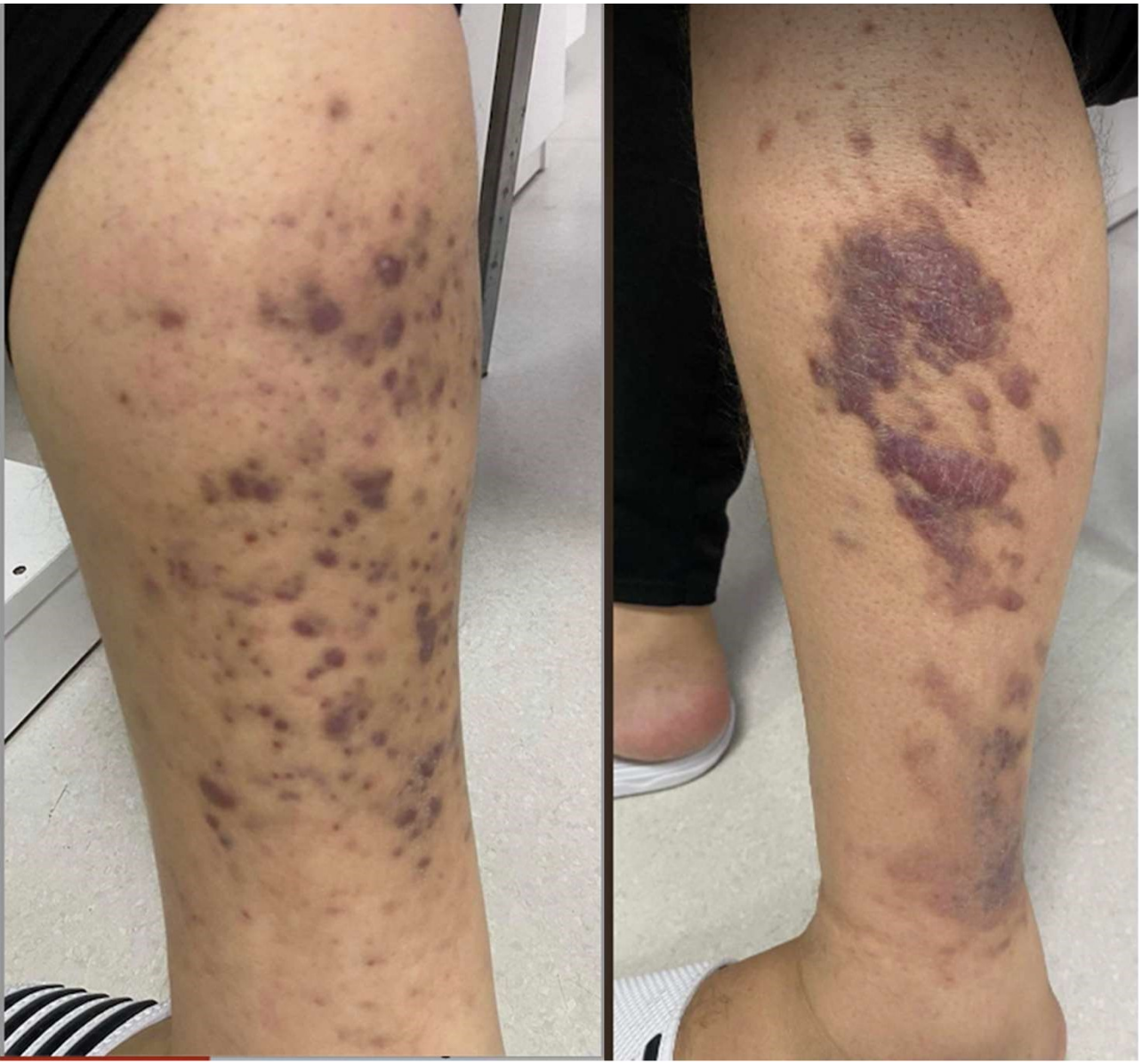
- Kidney Allograft biopsy: Chronic active antibody mediated rejection + De novo PLA2 negative Membranous Nephropathy

- g3, ptc2, C4d1, cg 1b, mm1, v0, cv2, i1, t1, ci1, ct1, ah 2

- July 2022- Serum Creatinine- 2.4 mg/dl, albumin- 22g/l, uPCR-12 mg/mg Creat

- Recommended Treatment: PE and IVIG

- No treatment was performed due to financial issues



- September 2022 patient - worsening of proteinuria and kideny function, angiomatous lesions affecting the legs and causing lymphedema,
- Kaposi sarcoma?
- 1st therapeutic decision : MMF was replaced by Everolimus (target blood concentration 6 ng/ml), tacrolimus was reduced (target tacrolimus level 4 ng/ml),
- biopsy of affected skin tissue: Kaposi sarcoma
- PET Scan did not reveal visceral Involvement
- HIV negative

- December 2022 patient was consulted by oncologist- administration doxorubicin based chemotherapy
- February 2023 discontinuation of doxorubicin
- February 2023 IVIG was reccomended

- June 2023: chief compliants: weight loss (10 kg), low grade fever, diffuse angiomatous lesions affecting the legs, generalized edema, dyspnea
- Labs:Creatinine -3.4 mg/dl GFR-22 ml/min/1,73m^2 (CKD-EPI 2021, serum albumin- 19g/l, urine protein creatinine ratio- 16.177, HB-7 g/dl, WBC-17x10^9/L, Ferritin >1000 ng/ml, TSAT-35%, CRP-280mg/l, Blood culture-sterile
- Treatment: Methilprednisolone 2mg, Everolimus 0.75 b.i.d (blood level 5.5 ug/l), tacrolimus 1.5 b.i.d (blood level 4 ng/ml), erythropoietin - 20,000 units/week

Problem list:

- Failed kidney allograft
- Severe Nephrotic syndrome
- Chronic inflammation
- ESA hyporesponsiveness
- Diffuse angiomatous lesions affecting the legs
- Generalized edema

Plan:

1.Discontinuation of the immunosuppressive Treatment

2. Start RRT- hemodialysis

3. transplant nephrectomy

- July 5, 2023 – HD initiation with av fistula (created before transplant still functioning)
- July 5, 2023 **Discontinuation of the immunosuppressive Treatment** **except of methylprednisolone**
- 24 July 2023- Transplant Nephrectomy

LABORATORY RESULTS BEFORE AND AFTER DISCONTINUATION OF THE IMMUNOSUPPRESSIVE TREATMENT AND TRANSPLANT NEPHRECTOMY

Before

- Creatinine -3.4 mg/dl GFR-22 ml/min/1,73m^2 (CKD-EPI 2021),
- Serum albumin- 19g/l,
- urine protein creatinine ratio- 16.177,
- HB-7 g/dl,
- WBC-17x10^9/L,
- Ferritin >1000 ng/ml,
- TSAT-35%,
- CRP-280mg/l,

After

- Serum albumin-36g/l,
- HB- 10.0 g/dl,
- WBC-4.5x10^9/L,
- Ferritin-267 ng/ml,
- CRP- 0.3mg/l,

➢ Current treatment: Methilprednisolone 2mg, HD 4-5 hours per session -three sessions per week , erythropoietin - 8,000 units/week

2 month later after Discontinuation of the immunosuppressive Treatment

Malignancy after solid organ transplantation:

Risk factors for cancer development after transplantation:

Risk factors for cancer development

Risk factors shared by patients in the general population :

- Age,
- Male sex,
- Smoking,
- Prolonged sun exposures,

- **Specific risk factors-for transplant populations:**
  - Type, extent, and duration of Immunosuppression;
  - duration of dialysis before transplantation
  - acute rejection
  - sensitization status
  - Coexisting viral infection (EBV, HHV-8, HPV, MCV)

Types of skin cancer in solid organ transplant recipients:

- Cutaneous squamous cell carcinoma (cSCC),
- Basal cell carcinoma (BCC),
- Melanoma,
- Kaposi sarcoma

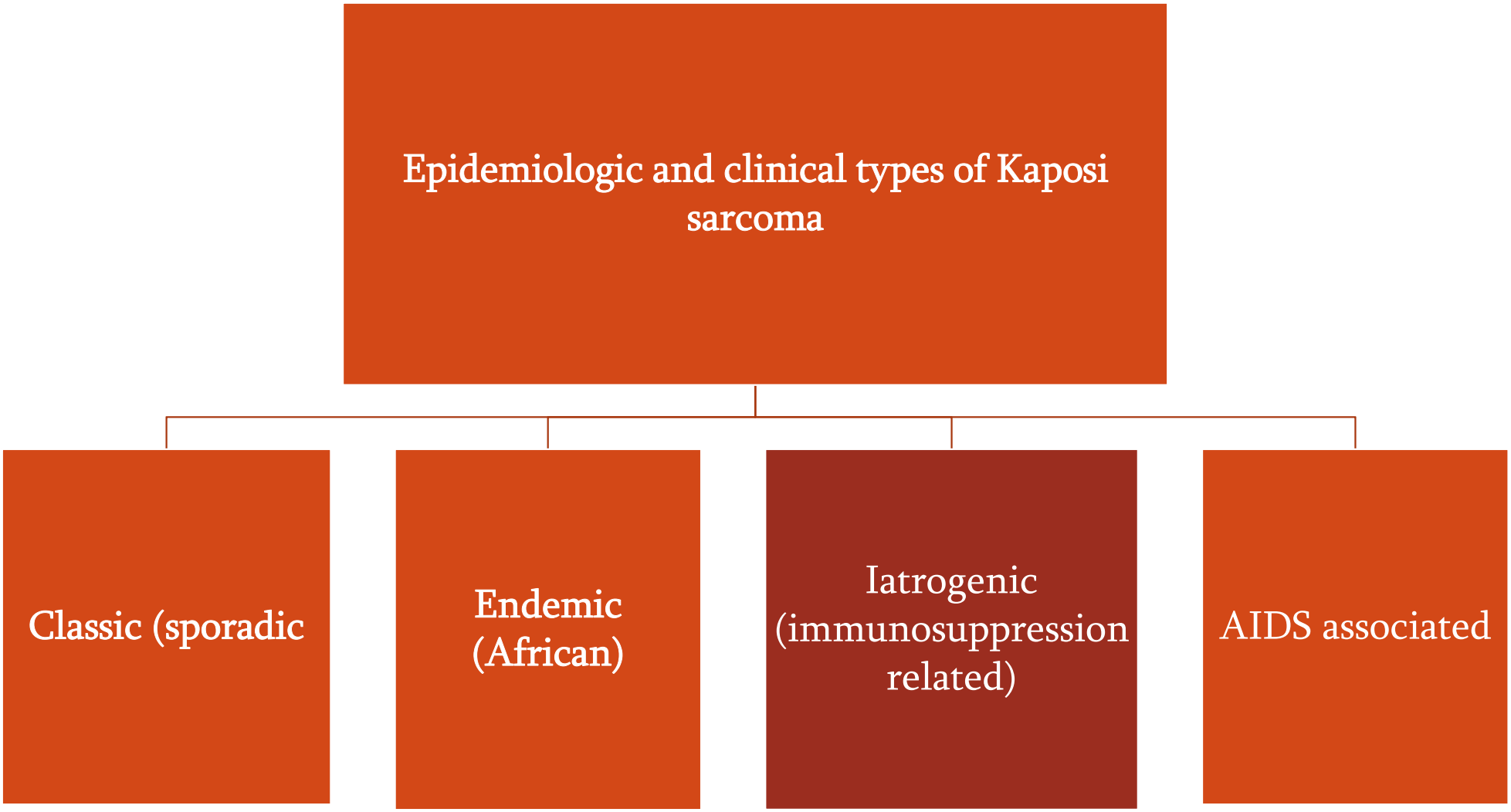
Proposed mechanisms -contribute to the development of skin cancer:

- Reduced immune surveillance, thereby facilitating the survival and proliferation of atypical cells.
- Direct or contributory carcinogenic effects of immunosuppressive agents
- Proliferation of oncogenic viruses in the setting of immunosuppression: EBV, HPV, KSHV, HTLV-1, MCPyV
- Mutations in the genes coding for the glutathione S-transferase family of proteins and the gene coding for *IRF4*

Epidemiology and risk factors for skin cancer in solid organ transplant recipients:
AUTHORS:Thomas Stasko, MDAllison M Hanlon, MD, uptodate.com

Common Viral-associated cancers in patients with suppressed immune system:

- Kaposi sarcoma (human herpesvirus 8),
- PTLD (Epstein– Barr virus [EBV]),
- lip and anal cancers (HPV)


Epidemiologic and clinical types of Kaposi sarcoma
Classic (sporadic
Endemic (African)
Iatrogenic (immunosuppression related)
AIDS associated

Iatrogenic (immunosuppression related) Kaposi sarcoma

Iatrogenic (immunosuppression related)	
Predominant risk groups	Exogenous immunosuppression, individuals of Mediterranean, Jewish, Arabic, Caribbean, or African descent; male to female ratio 3.3:1, average age at diagnosis is 43 years The average time to presentation is 13 to 21 months following ransplantation
Cutaneous presentation	Distal lower extremities; may be disseminated (90% -cutaneous and/or mucosal lesions, and lesions on the lower extremities)
Visceral involvement	Relatively common 25 to 30 % of KTR and 50 % of heart or liver transplant recipients
Clinical course	May regress with modification of immunosuppression; May be aggressive

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CLINICAL FEATURES

Skin lesions

- purplish, reddish blue, or dark brown/black macules, plaques, and nodules on the skin
- lesions range in size from very small to several centimeters in diameter,
- accompanying lymphedema of the affected extremity

Extracutaneous involvement

- mucous membranes of the mouth and GI tract,
- Regional nodal involvement is relatively uncommon
- Involvement of visceral organs other than the lining of the GI tract (eg, lung, liver, bone, bone marrow) is extremely rare

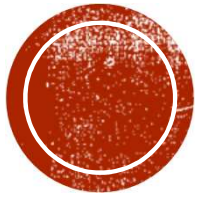
Biopsy of affected skin tissue:

Histological features:

- Initially- proliferation of capillaries sprouting from normal vessels,
- Later - large vascular spaces in the dermis associated with proliferation of spindle cells.
- PCR skin lesions to detect amplified human herpes virus 8 (HHV-8) DNA sequences,
- immunohistochemical staining of biopsy specimens -to detect the presence of HHV-8 latency-associated nuclear antigen (LANA-1) within the spindle cells

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients

Chapter 20: Managing Cancer with Reduction of Immunosuppressive Medication



20.1: We suggest consideration be given to reducing immunosuppressive medications for KTRs with cancer. (2C)

20.1.1: Important factors for consideration include (Not Graded):

- the stage of cancer at diagnosis;
- whether the cancer is likely to be exacerbated byimmunosuppression;
- the therapies available for the cancer;
- whether immunosuppressive medications interfere with ability to administer the standard chemotherapy

20.2: For patients with Kaposi sarcoma, we suggest using mTORi along with a reduction in overall immunosuppression. (2C)

American Journal of Transplantation 2009; supplement 3: vol 9,

Transplant International 2021; 34: 1789–1800

Transplant International

REVIEW

Managing immunosuppressive therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer): an overview of the available evidence and guidance for shared decision-making

Rachel Hellemans[1,2], Liset H.M. Pengel[3], Sylvain Choquet[4], Umberto Maggiore[5] & for ESOT Workstream 3 of the TLJ (Transplant Learning Journey) project

Question 1: Should we decrease the overall anti- rejection therapy in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

Question 2: Should we switch to mTORi in potentially cured post-kidney transplant cancer (excluding non-melanoma skin cancer)?

Question 3: Should we switch to an immunosuppressive regimen with mTORi and low-dose CNI?

SUMMARY: INFORMATION TO GUIDE SHARED DECISION-MAKING

Potential benefits and risks of the strategy of reducing overall maintenance anti-rejection treatment :

- Traditional approach used for KTRs with a history of non-skin cancer treated with a curative intent.
- This approach needs to be balanced carefully against the risk of allograft rejection and graft loss.
- Reduction in trough blood levels

traditional lower bounds might be the most effective strategy to prevent cancer recurrence, but also the least safe strategy to prevent rejection – especially if that occurs early after transplantation

Potential benefits and risks of the strategy of switching from CNI to mTORi

- The strategy of replacing the CNI with a mTORi could be an effective strategy in preventing recurrence of cancer, although the current available evidence on efficacy mainly concerns non-melanoma skin cancers and Kaposi sarcomas.
- mTORi anti-cancer effect is dose-dependent
- mTORi dosage that is most effective against cancer is often poorly tolerated
- There is also some evidence that conversion from CNI to mTORi could be associated with an increased risk of developing chronic rejection, although reports have shown mixed results: the risks may be limited in well-selected patients providing that the concomitant medication (MMF and steroids) is sufficiently strong

Potential benefit and risks of the strategy of switching from CNI + MPA/MMF to CNI + mTORi

- The strategy of replacing the MMF/MPA with a mTORi (EVL target 5.5 ng/ml) while keeping the CNI at low doses (target Tac, 4 ng/ml; target CsA, 50 ng/ml) might be safer in terms of risk of rejection, and of adverse effects,
- strategy of replacing MMF/MPA with a mTORi showed:

1) the benefit in reducing the risk of non-skin cancer may be similar, but is currently far less documented than the strategy of replacing CNI with mTORi, especially under the current low-dosage EVL regimes;
2) There is no increased risk of rejection, graft loss or mortality;
3) mTORi is better tolerated.

Transplant International 2021; 34: 1789–1800

Conclusion:

- KS may respond to reduction or discontinuation of the immunosuppressive regimen, and this should be the first therapeutic maneuver
- The strategy of replacing the MMF/MPA with a mTORi might be safer in terms of risk of rejection, and of adverse effects in patients with Kaposi Sarcoma
- In patients who don't respond to reduction of immunosuppressive regimen discontinuation of the IS treatment can be chosen as a life saving strategy