Skin Containing VCA as a Monitoring Tool for Intestinal Transplantation

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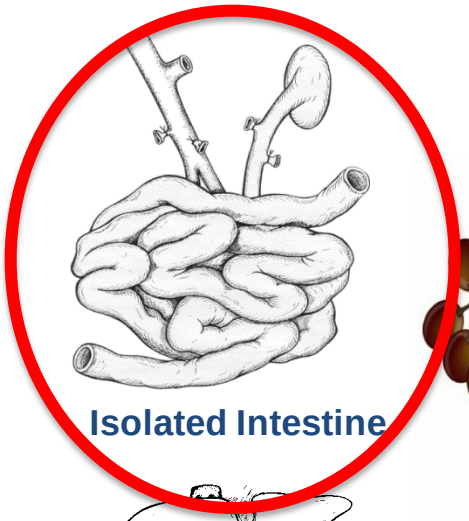
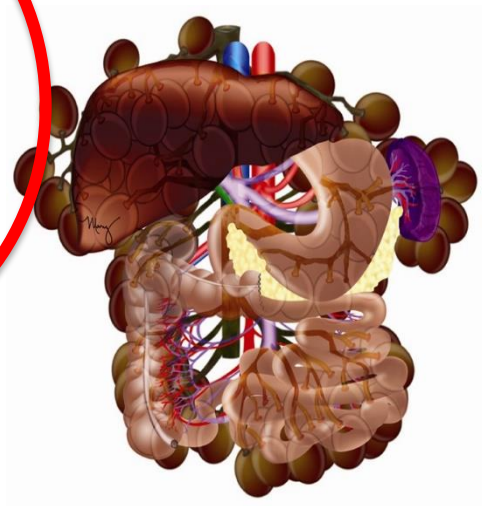
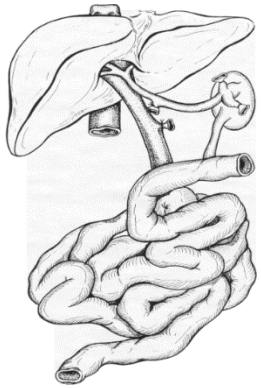
Intestinal Transplants

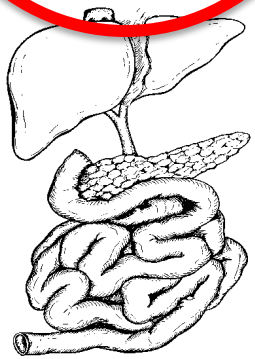


Isolated Intestine

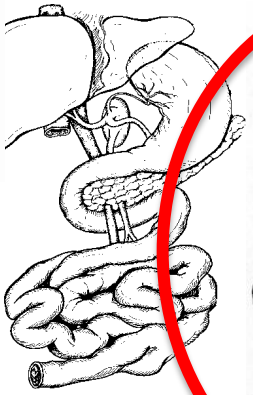




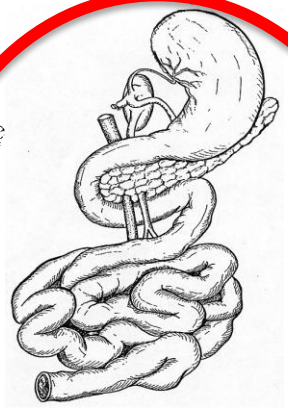
Liver and intestine



Liver, intestine and pancreas

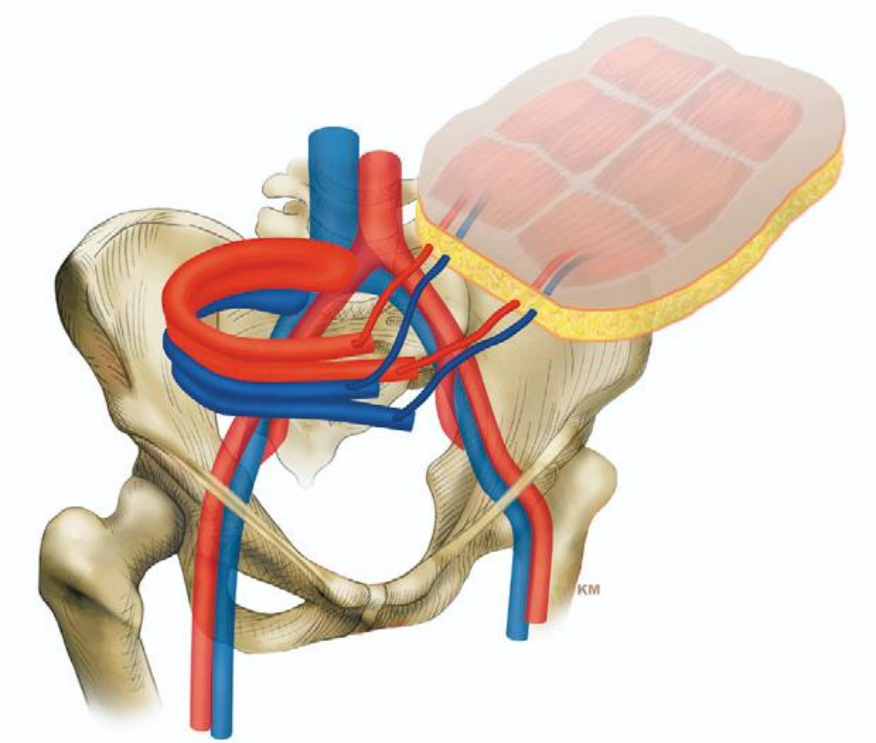


Multivisceral



Modified MVT

Abdominal Wall Transplant

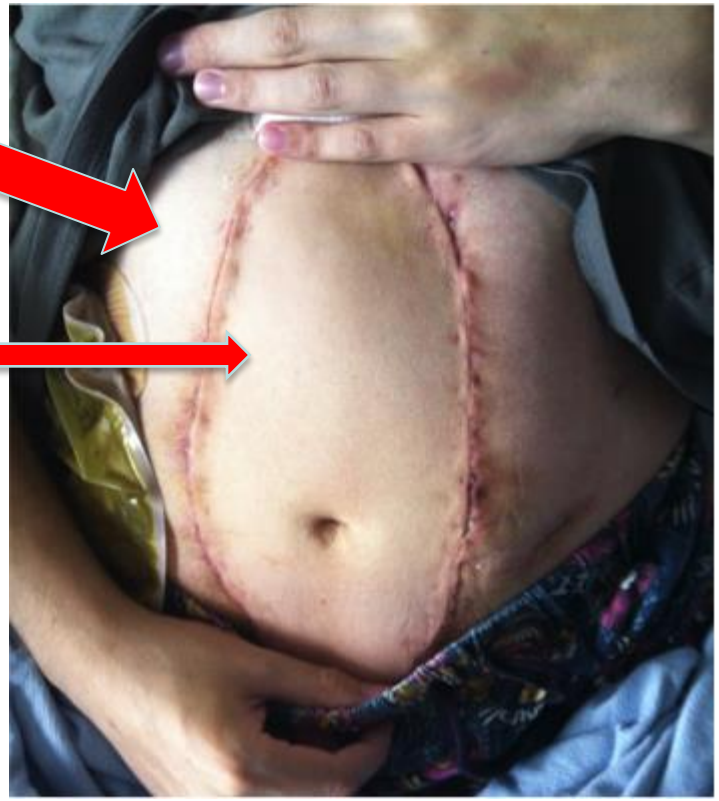


Transplantation of the abdominal wall.
Levi et al, Lancet. 2003 Jun 28;361(9376):2173-6.

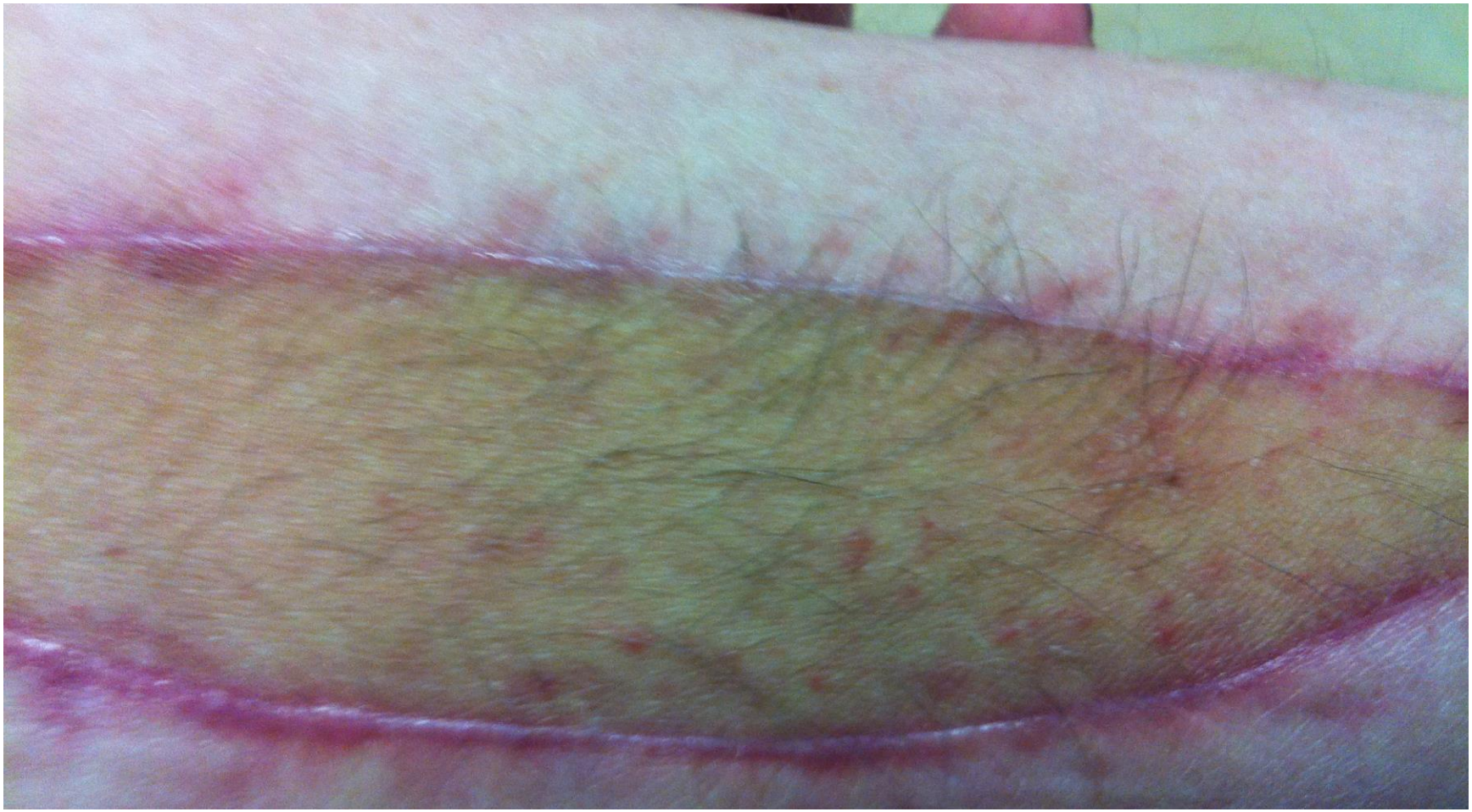
Small Bowel Transplant

Abdominal Wall Transplant

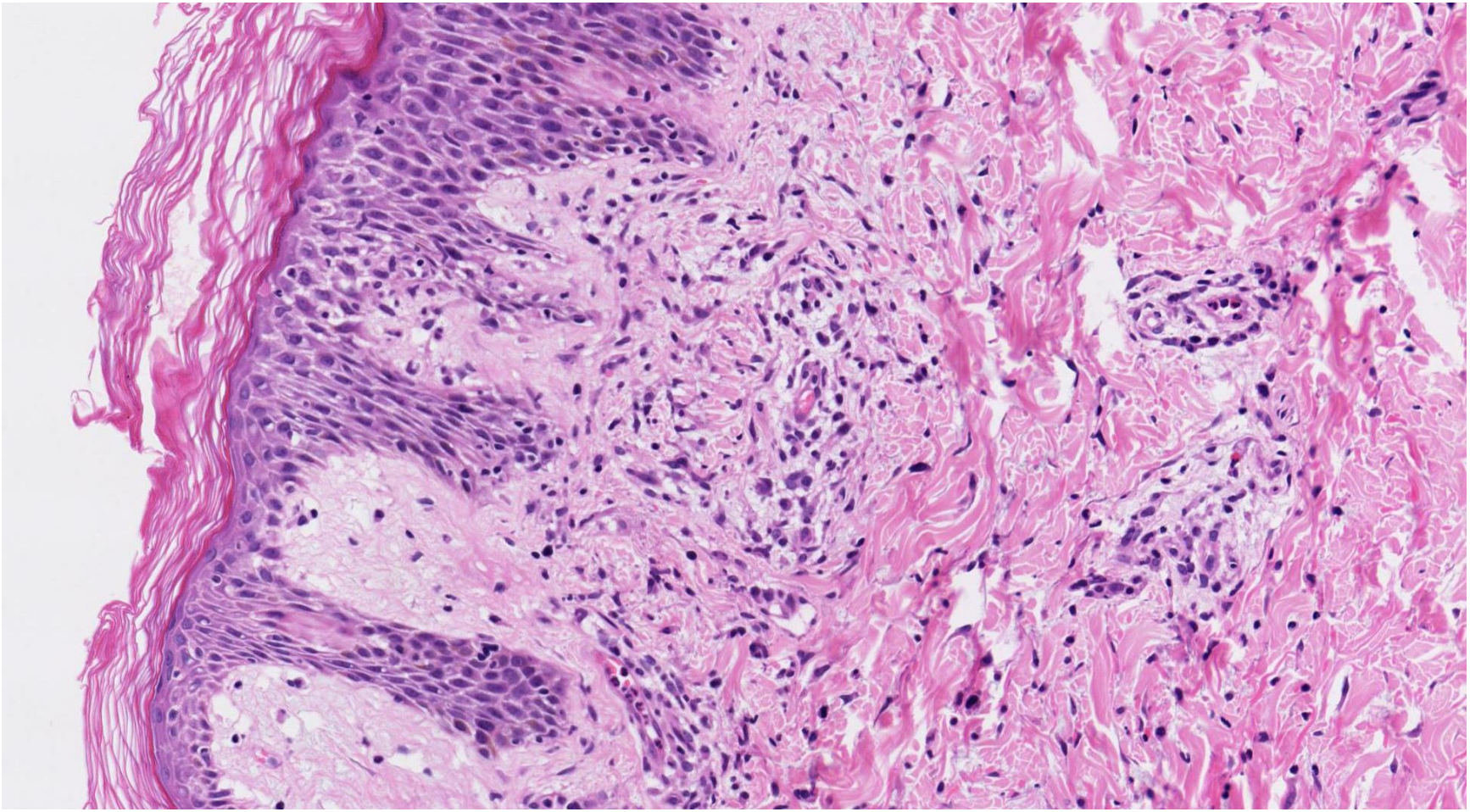
Dynamic ‘Canvas’



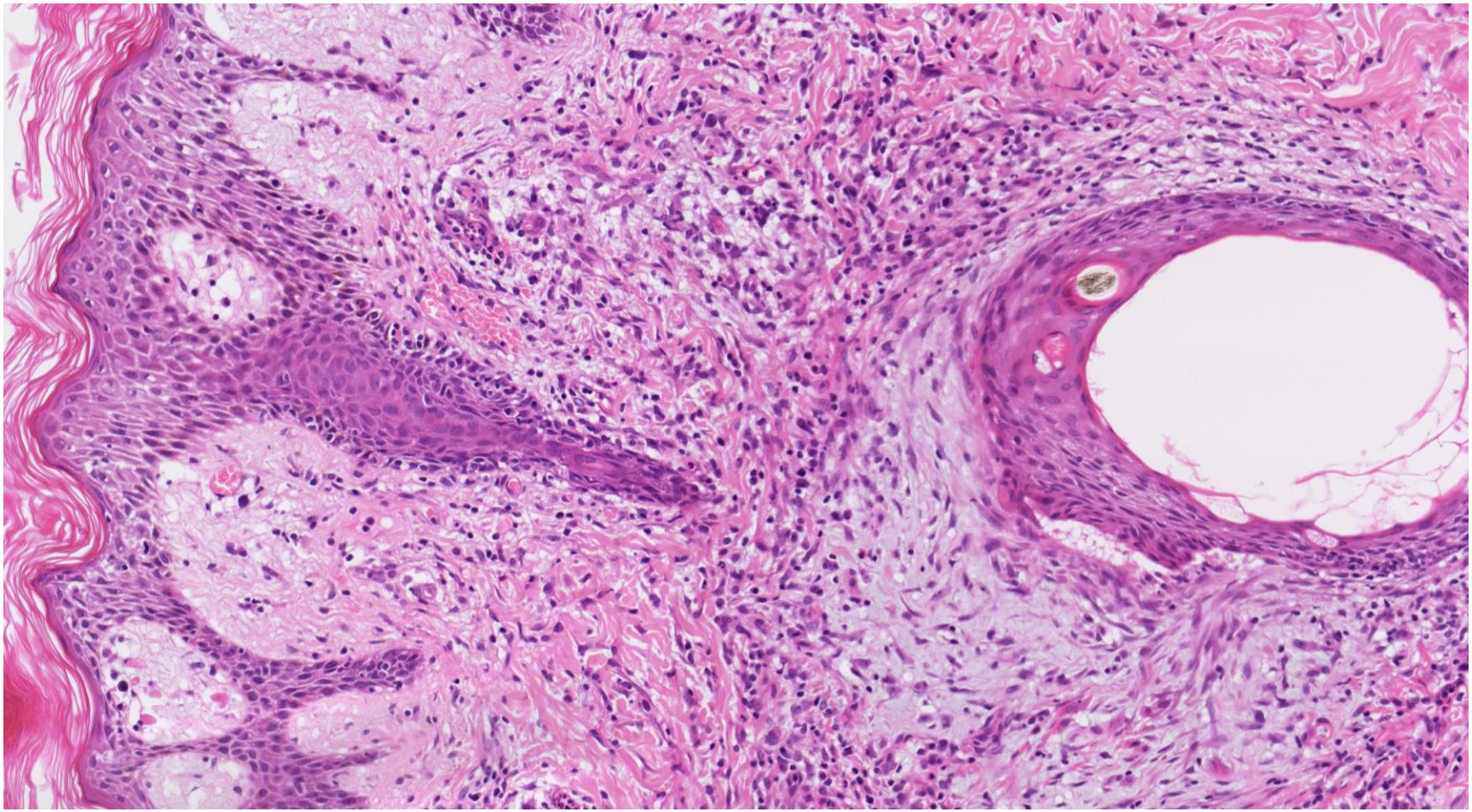
Sentinel Skin Graft Rejection



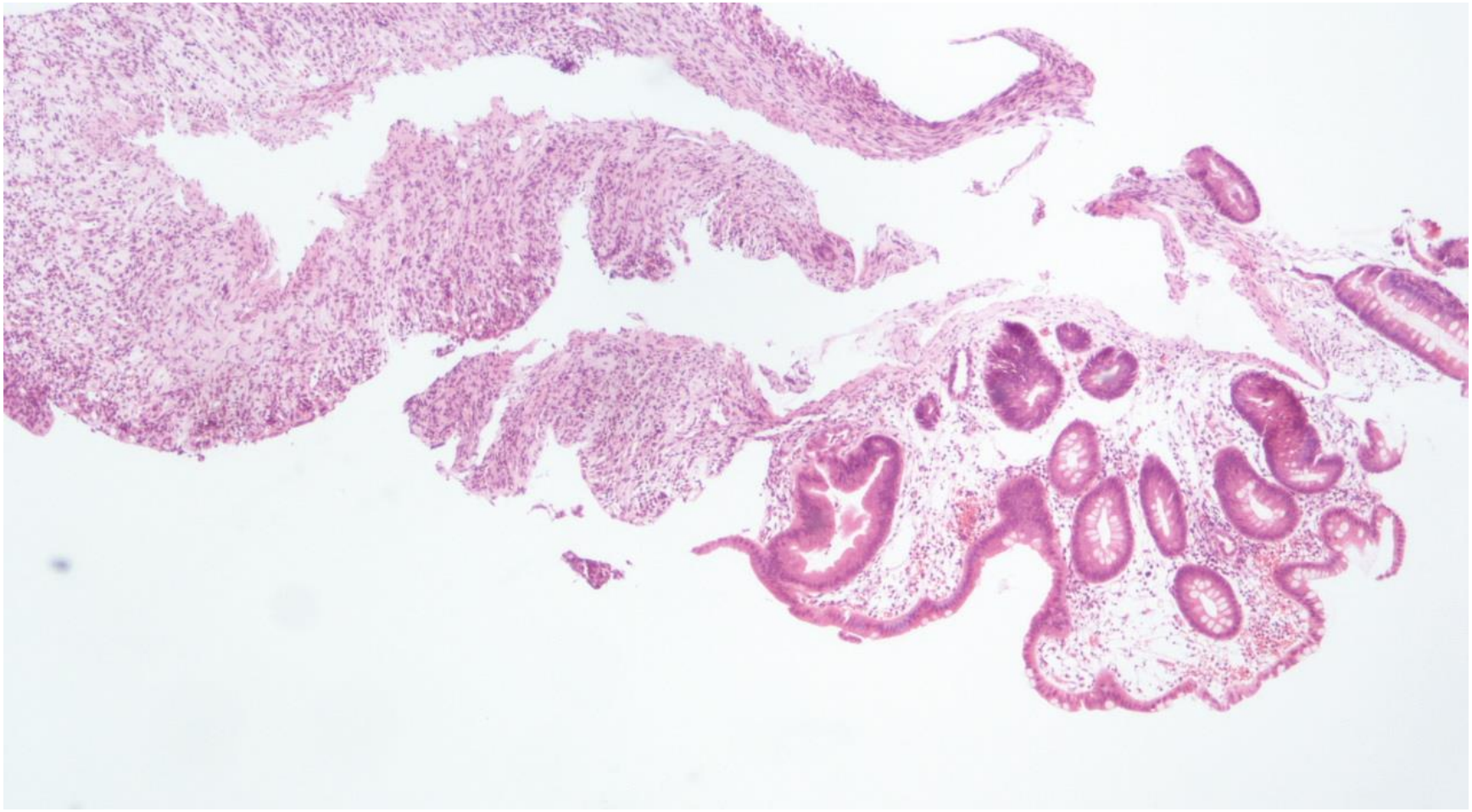
Punch Biopsy of Skin



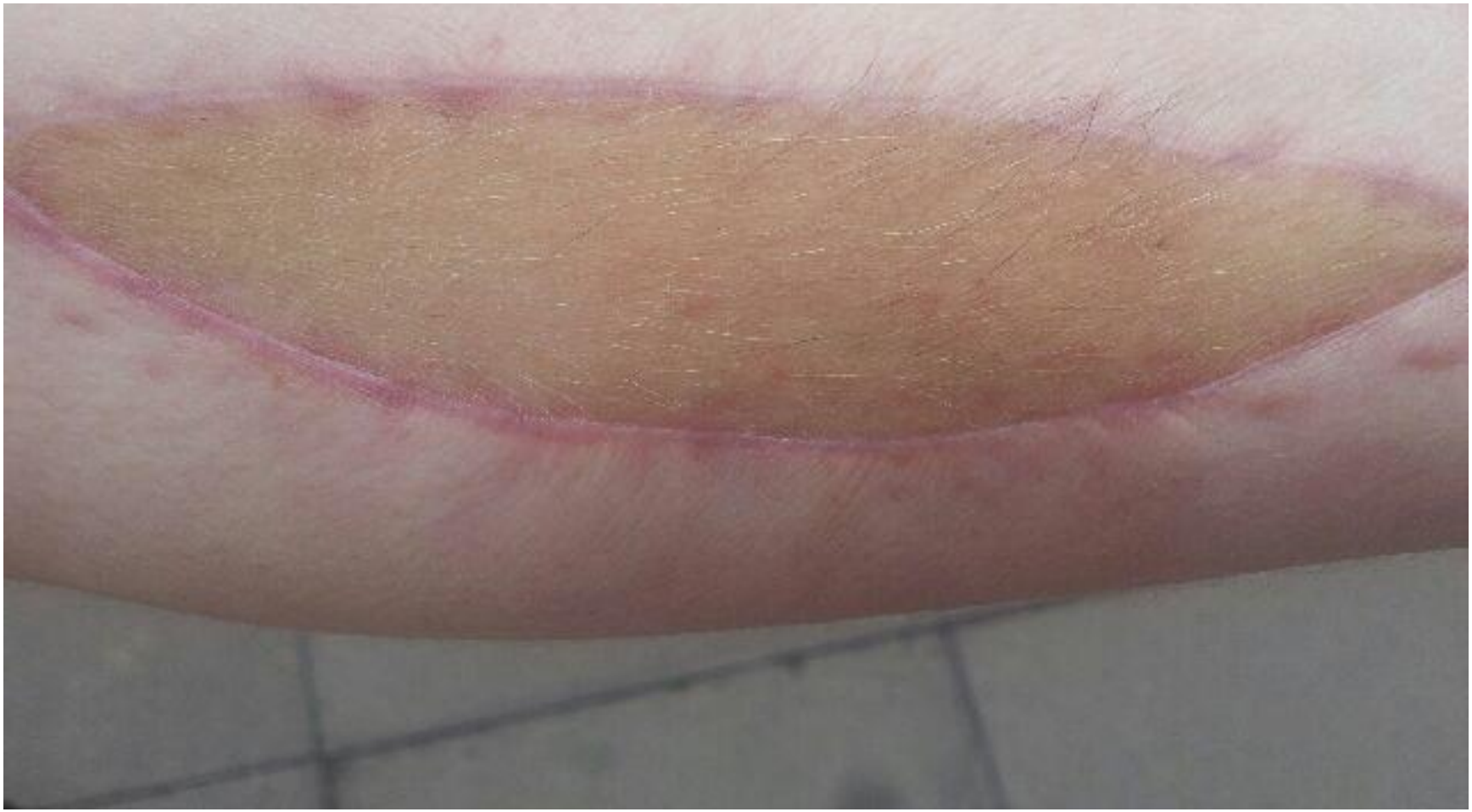
Interface Spongiosis



Histology of Bowel



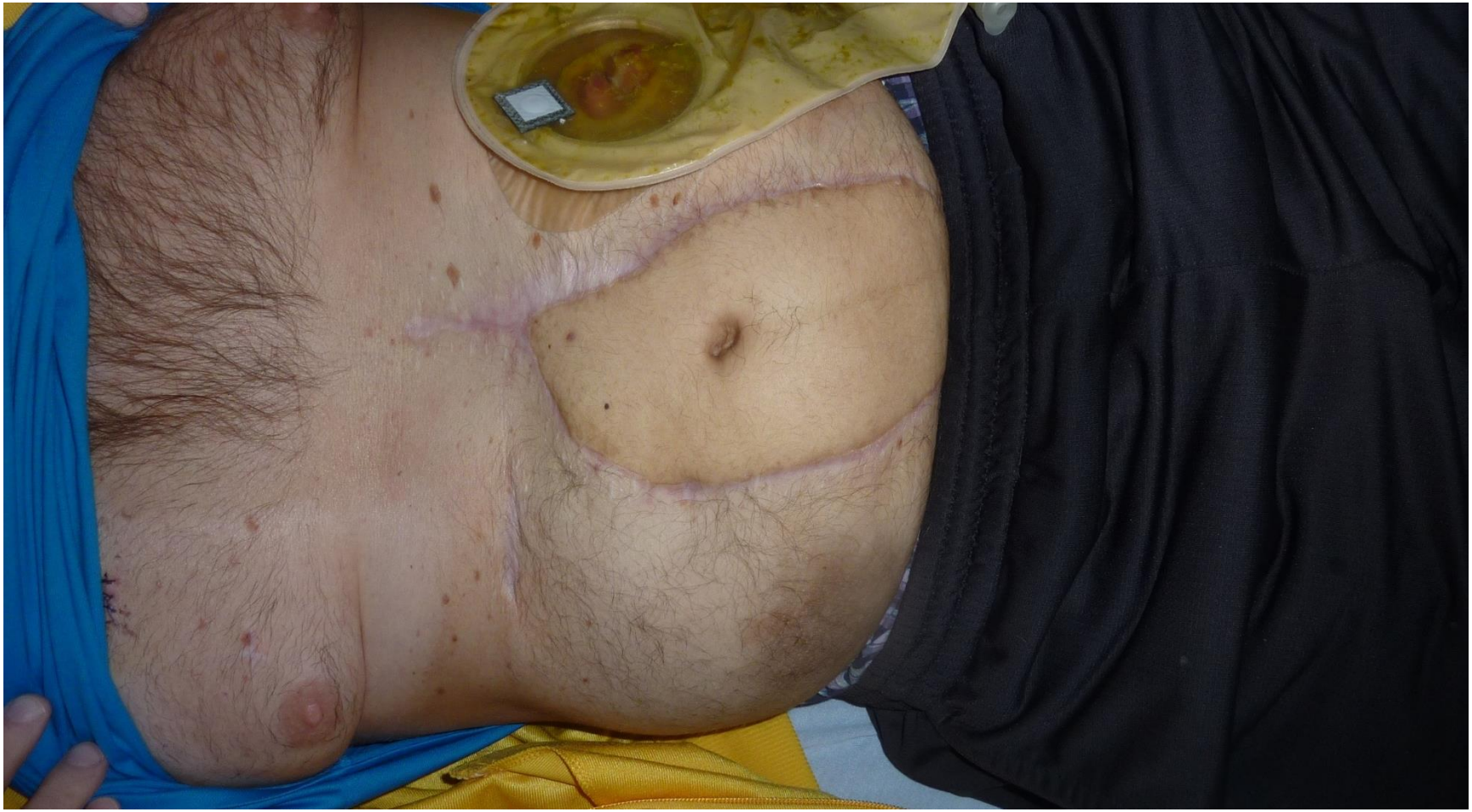
Sentinel Skin Graft after Treatment



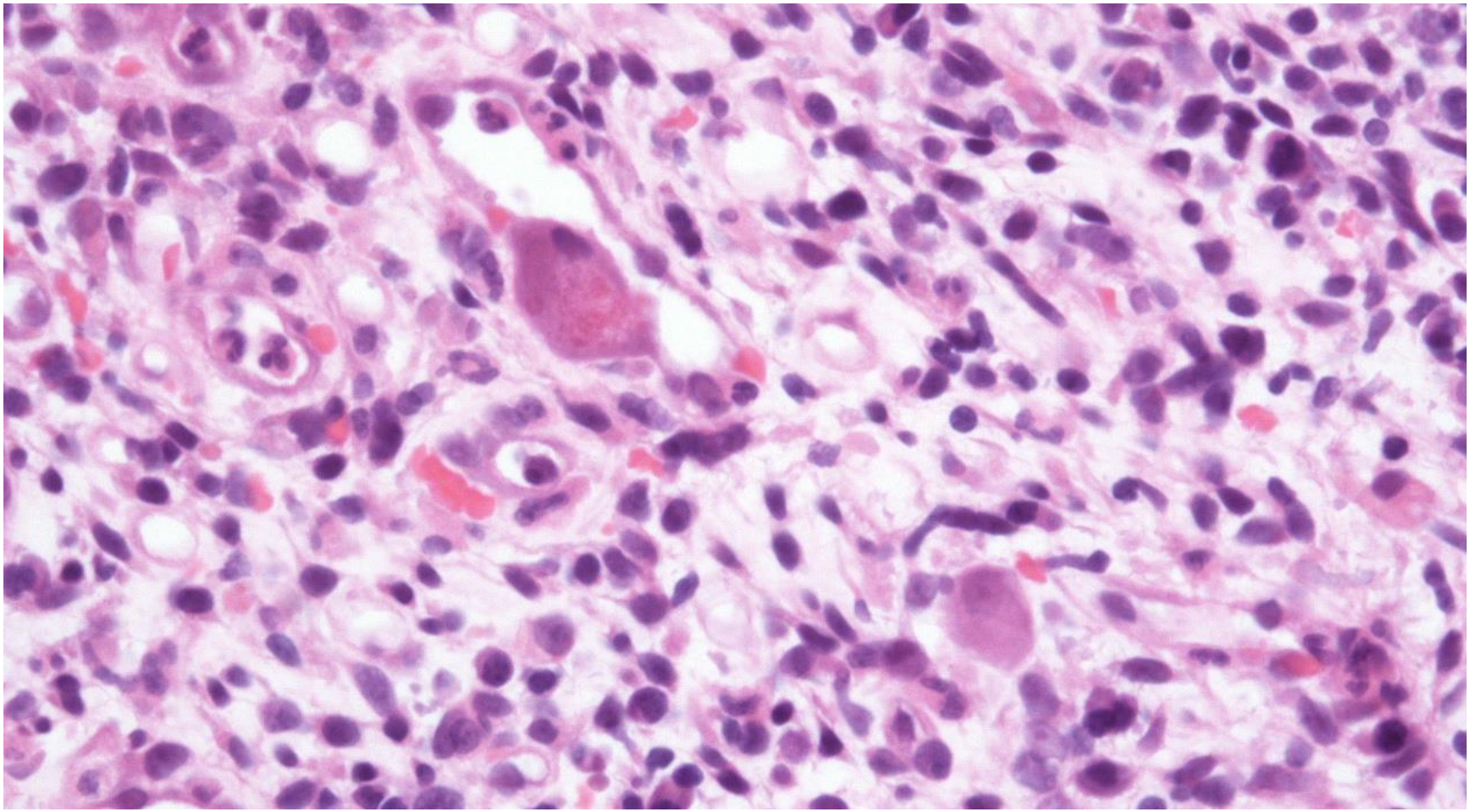
A Case of Intrigue

- Presented with acute bowel dysfunction 25 days after the last pulse of steroids
- Stoma output > 40mls/kg/24 hours
- Abdominal wall graft was normal
- Endoscopy revealed flattening and patchy loss of villi architecture
- Histology was reported as moderate rejection

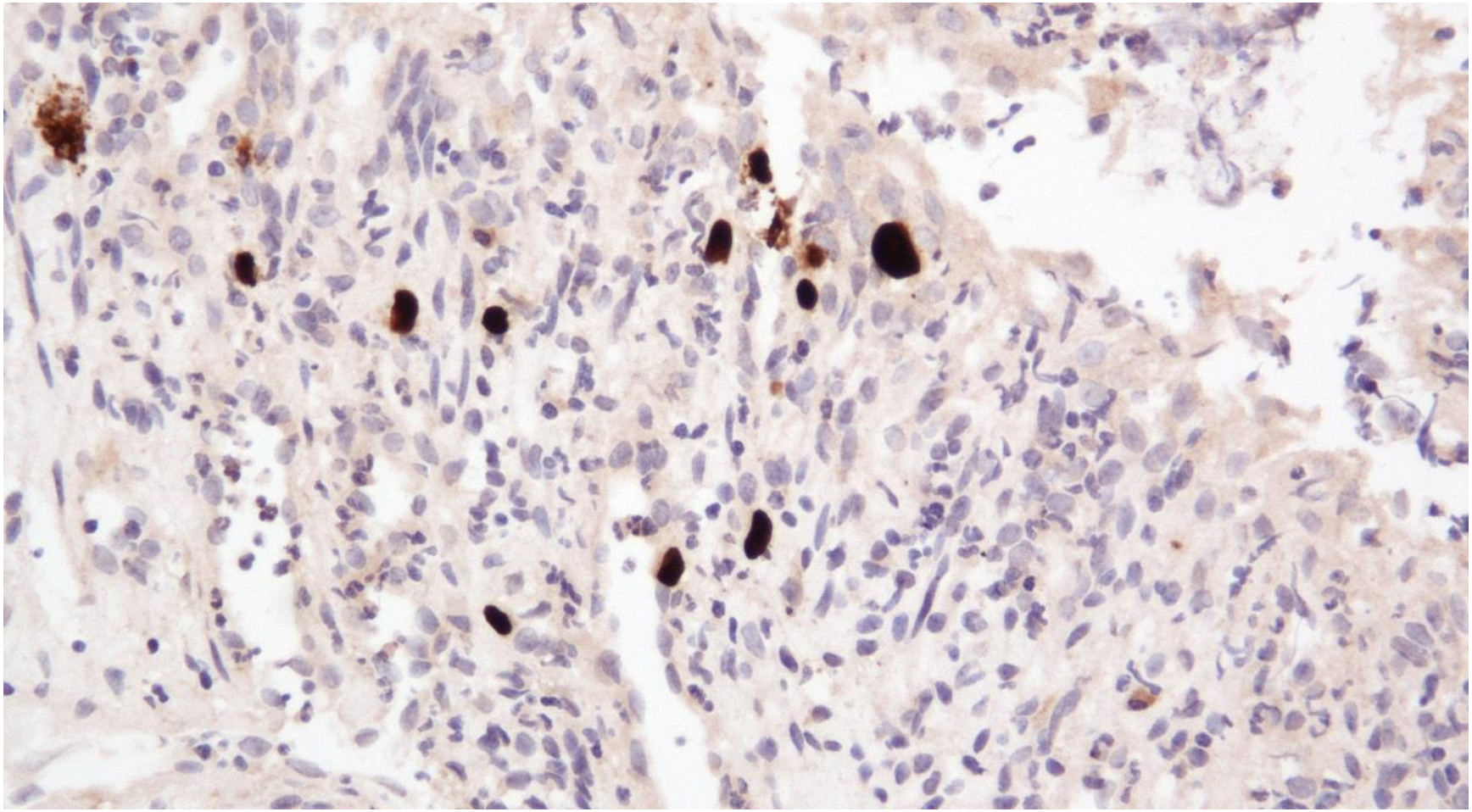
Abdominal Wall - visual



CMV Inclusion Bodies



CMV Immunohistochemistry



On-going Rejection?

- Not treated with increased immunosuppression based only on the appearance of the abdominal wall skin
- Subsequent immunohistochemistry on the bowel mucosa highly positive for CMV
- No evidence of CMV viremia
- Treated for CMV disease
- Resolution of bowel dysfunction

Lesson Learned

- The skin of the abdominal wall graft was an accurate indicator of immunologic activity in the bowel graft
- Appropriate antiviral therapy was directed after the immunohistochemistry report
- Original diagnosis of rejection was overturned by the pathologist
- Increase in immunosuppression in this case potentially would have led to either graft loss or death due to CMV

Analysis of Oxford ITx and VCA Patients

- Does the addition of a VCA increase the immunological burden?
- Does VCA increase the incidence of de novo DSA?
- Do de novo DSA have an impact on graft survival?

Pre-Transplant Nationally agreed Risk Stratification

Based on results from most recent sample

Risk level	cMFI	Risk of rejection
1	No detectable DSA	**Standard risk**
2	< 2,000	**Low risk** Minimum risk of hyperacute rejection > Standard risk of rejection
3	2,000 - 8,000	**Medium risk** Flow cytometry crossmatch likely to be positive Low risk of hyperacute rejection Intermediate risk of humoral rejection
4	> 8,000	**High risk** CDC crossmatch likely to be positive High risk of humoral rejection Transplant veto, except for exceptional cases

Laboratory Investigations

Pre-transplant HLA antibody profile

- 3 monthly or monthly if sensitised
  - Antibody screening and specificity analysis: Luminex technology
  - Identify unacceptable HLA antigens pre-transplant
  - Calculated HLA antibody Reaction Frequency (cRF%):
    % HLA incompatible, blood group compatible, UK donors in a pool of 10.000

Time of transplant: Crossmatch

  - Complement dependant cytotoxicity (CDC) and flow cytometry (FC)

Post-transplant HLA antibody monitoring

- 1,3,6,9,12 months post transplant, annually and at clinical events
  - Antibody screening and specificity analysis: Luminex technology

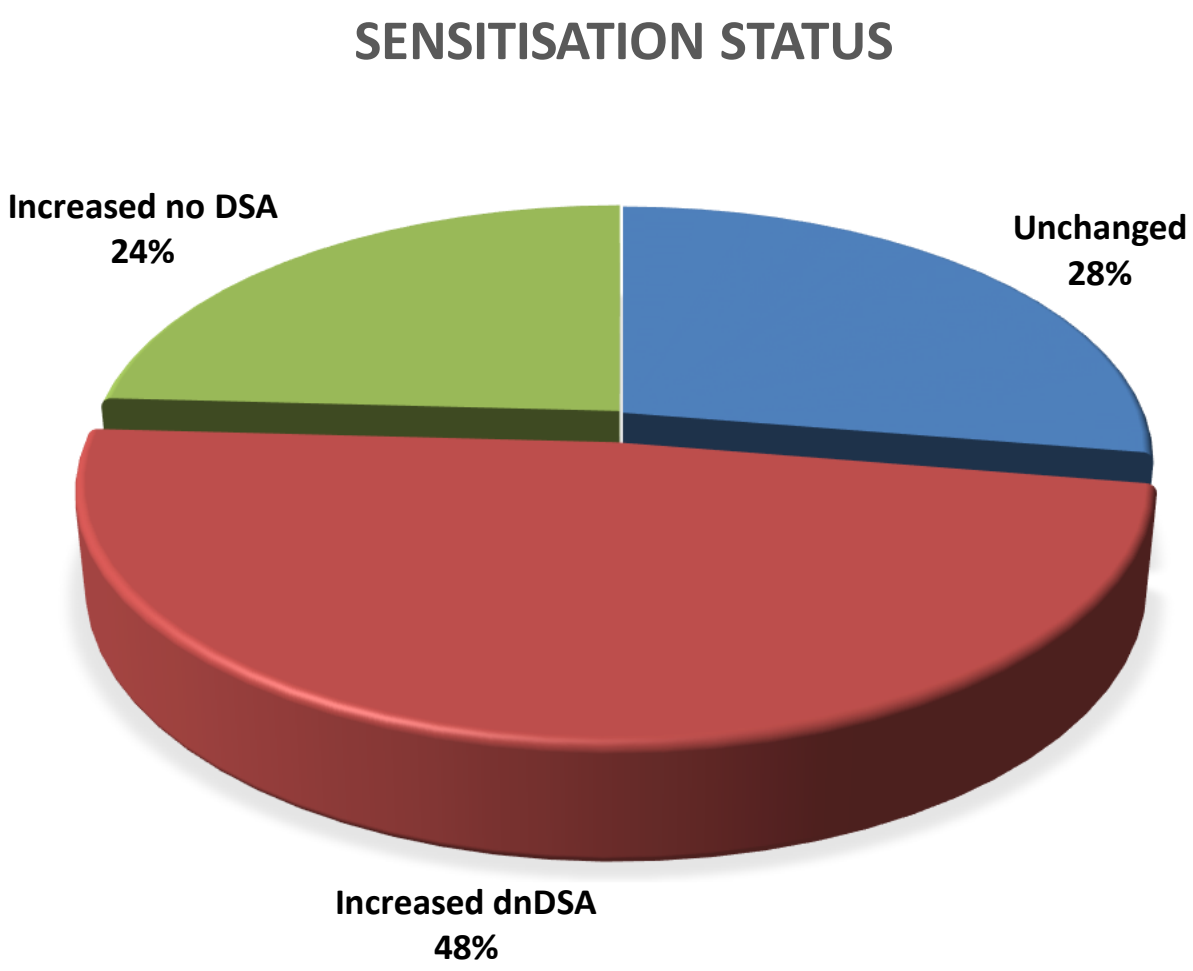
Oxford Transplant Cohort

- 2008 – 2015
  - 32 patients
    - 14 ITx without a VCA
    - 18 ITx with a VCA
  - Overall Graft Survival
    - 1 year: 86%
    - 5 years: 49%

Oxford Transplant Cohort n=32

- Sensitisation status pre transplant
  - 19 Unsensitised patients
  - 11 Standard risk, no DSA, crossmatch negative
  - 2 Higher Risk Transplants, DSA +ve
    - 1 -High risk: Bw4, DR16, DQ5, cMFI 19.000
      - CDC-ve, FCXM +ve, SPA +ve
    - 1 -Medium risk: DP*04:01, cMFI 3.200
      - CDC and FCXM -ve, SPA +ve

Post-transplant HLA Sensitisation Status
29 patients monitored



Transplanted Cohort

DBD

- **24** SBTx → VCA n=12 (50%)
- **8** MMVTx → VCA n=6 (75%)

Rejection

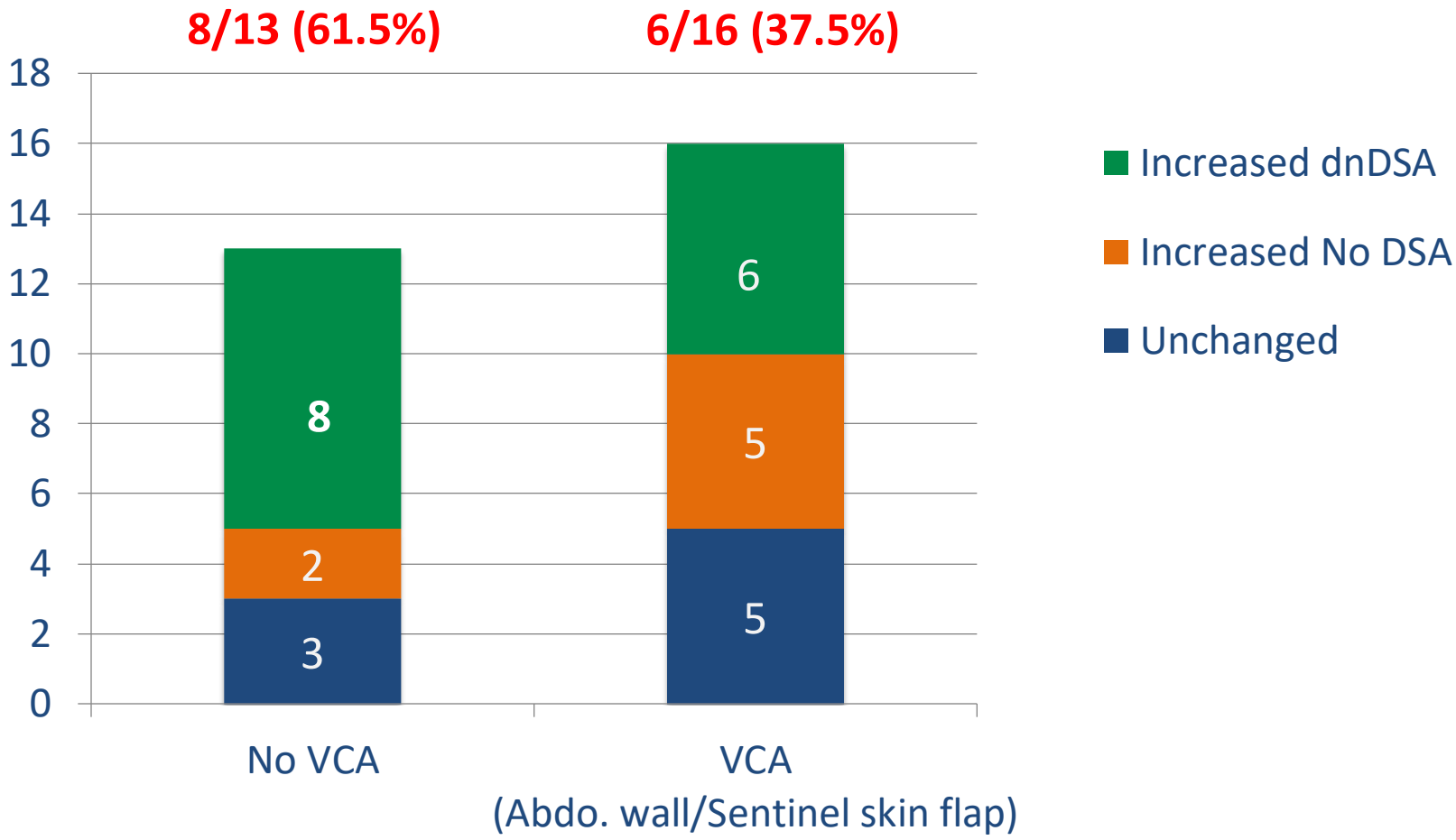
- **5 ITx rejection** episodes in ITx only
  (5/14, 35.7%)
- **3 ITx rejection** episodes in ITx+VCA
  (3/18, 16.7%)
- **7 Skin rejection** episodes in ITx+VCA
  (7/18, 38.9%)
- **NO** bowel rejection without skin rejection!

Donor Specific Antibodies

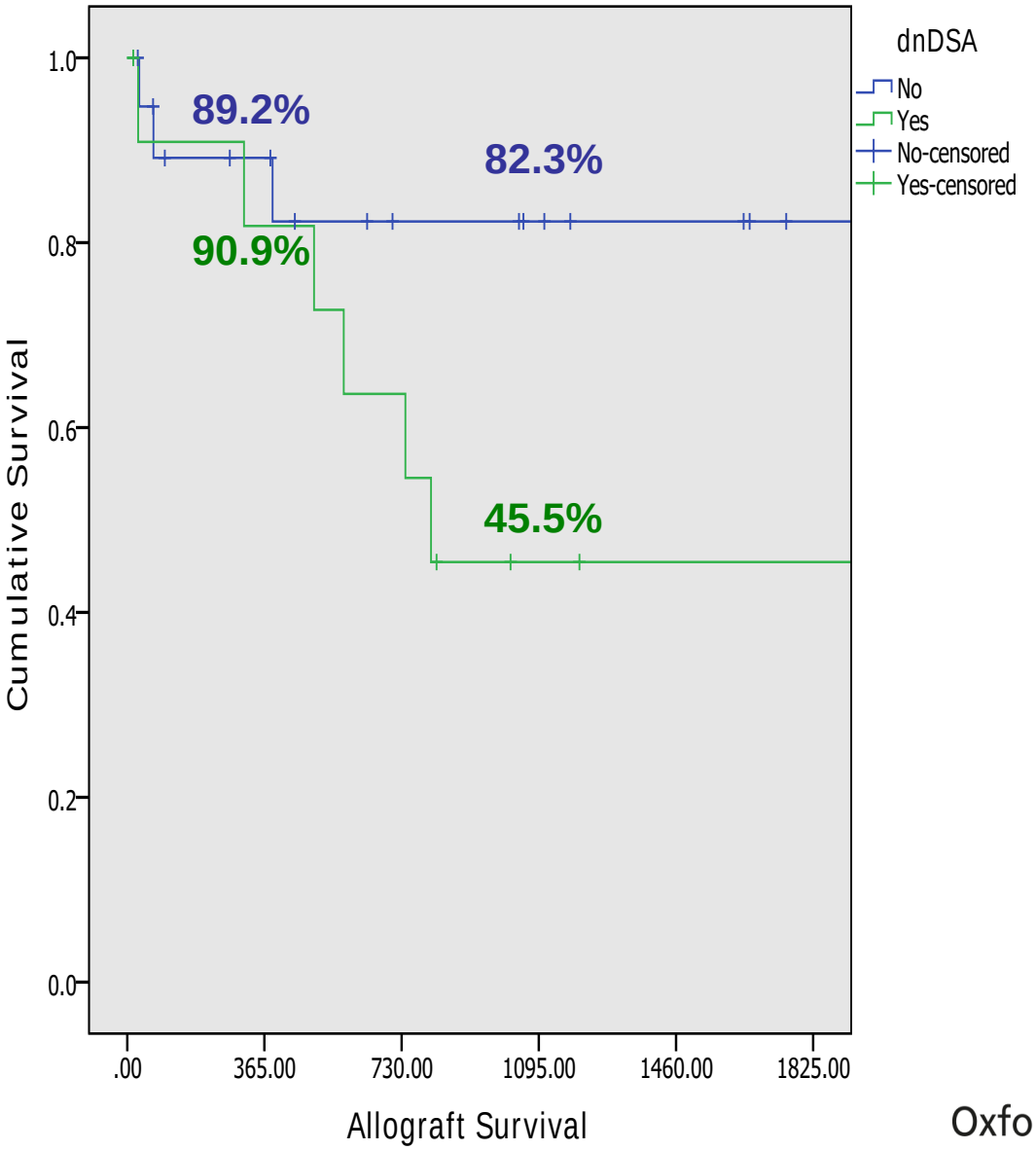
- Pre Tx DSA 2/32 (6.3%)
- Post Tx 14/29 (48%) developed dnDSA
  - 4 class I alone
  - 3 class II alone
  - 7 class I & class II
  - Mean MFI of class I dnDSA: 7628±10661 SD
  - Mean MFI of class II dnDSA :10721±18657 SD

Post Transplant Sensitisation

De novo DSA post transplant



Graft Survival stratified for *de novo* DSA



p=0.183

Results of the univariate Cox regression analysis to evaluate predictors for graft survival

Characteristic	Wald	HR	95% CI	*p* value
Recipient Factors				
Age at Tx	**4.766**	**1.061**	**1.006 - 1.118**	**0.029**
Donor Factors				
BMI donor	**4.864**	**1.568**	**1.051 - 2.338**	**0.027**
Transplant Factors				
VCA included	0.178	1.331	0.352 - 5.036	0.673
Existence of dnDSA				
dnDSA class I	0.240	0.577	0.064 - 5.200	0.624
dnDSA class II	3.263	4.247	0.884 - 20.391	0.071
dnDSA class I+II	**7.877**	**14.839**	**1.016 - 22.362**	**0.048**
dnDSA max MFI levels	3.384	1.000	1.000 - 1.000	0.066
dnDSA class I MFI levels	0.849	1.000	1.000 - 1.000	0.357
dnDSA class II MFI levels	**3.487**	**1.000**	**1.000 - 1.001**	0.062

Results of the multivariate Cox regression analysis to evaluate independent predictors for long term graft survival

Characteristic	Wald	HR	95% CI	*p* value
Recipient age at Tx	**7.668**	**1.189**	**1.052 - 1.344**	**0.006**
Existence of dnDSA	**8.135**			**0.043**
dnDSA class I	2.207	6.107	0.300 - 124.326	0.137
dnDSA class II	1.705	7.028	0.376 – 131.216	0.192
dnDSA class I+II	**7.912**	**45.306**	**3.178 – 645.875**	**0.005**

Summary

Skin containing VCA seems to be a future leader for diagnosis of rejection – sentinel skin

Combining an intestinal transplant with an abdominal wall VCA does not increase the incidence of *de novo* DSA

Multivariate analysis showed that the development of *de novo* DSA in intestinal transplantation is detrimental to the long-term survival of the graft

Questions

What are the next steps?

Do we have to treat as soon as we diagnose de novo DSA?

Which organ leads the decision?

What are the treatment options?

Thank You

Oxford Transplant Centre – Prof. Peter Friend

Transplant Immunology Laboratory – Prof. Susan Fuggle

Plastic, Reconstructive and Hand Surgery – Mr Henk Giele