A clinical scoping review exploring anaerobic bacteria, HPV and Mumps as possible contributors to testicular atrophy, infertility and malignancy

Tim Oliver, Jonathan Shamash,
Constantine Alifrangis,
Jack Cuzick, Dan Berney
Barts Cancer & Wolfson Institutes
London EC1M 6BQ

INTRODUCTION

Male infertility is a known risk factor for Testicular Germ Cell Tumour(TGCT)

Maternal intrauterine exposure to oestrogens and xeno-oestrogens is the primary factor linking TGCT and infertility (and world wide declining sperm counts and could be playing a role in increased cryptorchidism, hypospadias, rising incidence in sexual ambiguity and declining sexual activity in the younger generation).

Less discussed in epidemiology of TGCT is the role of 2nd "hits", influencing transition by clonal evolution from the oestrogen primed gonocytes after puberty to Testicular intra-epithelial neoplasia, seminoma and non-seminoma under the influence of raised FSH due to testicular atrophy.

While the extent of intrauterine exposure could well influence the degree of post-puberty atrophy, the past 30 years has demonstrated a number of post puberty "traumatic" events linked to TCGT occurrence. Hypo-vascular scars could favour colonisation by anaerobic bacteria causing cell damage, reducing time for DNA repair and accelerating malignancy clonal evolution.

It is the aim of this mini-poster to review the increasing evidence of anaerobic bacteria being a therapeutically reversible aetiological factor in post pubertal sperm count decline and the evidence that such "traumatic" events are involved in TGCT epidemiology by accelerating clonal evolution

Methodology:

This scoping review of oncogenic potential of anaerobic bacteria in TGCT wil focus first on how they are involved in Stomach, oral, cervix, pancreatic, penile and prostate cancer.

Then I will consider impact of "traumatic events" in epidemiology that have emerged from a 50 year experience of treating TGCT.

I will end by reviewing the bacteriology and virology of semen and it's impacts on infertility and how it synergises with the product of "traumatic events"

Cancers associated with anaerobic infection

Gastric ca & H. pylori treatment leads to reduced gastric cancer even in familial cases

Oral ca linked to anaerobic periodontal disease

Cervix ca linked to bacterial vaginosis (OR 2.91). Treating male reduces female BV incidence

Pancreatic Ca linked to oral Microbiome & mumps

Prostate Ca linked to puberty acquisition of C. acnes. 30+ years later found with other anaerobes in prostate cancer but less frequently in BPH and associated with raised PSA & lack of circumcision

Summary of prenatal and post-pubertal environmental and genetic factors in germ cell cancer Epidemiology

Prenatal Factors

Estrogens / Xenoestrogens.
Material Smoking (? And diet).
X linked gene (Xq27) and Cryptorchdism(?Estrogen).
C-kit gene mutation (Induced by excessive in-utero E).
Twins MZ>DZ same pathology
FH cancer NS>S

Diet:

High fat increase Xenoestrogenic exposure.
Low fat decrease vitamin A and D Producing immunosuppression.

Post Pubertal Factors

Increasing FSH / Cyclin D2 drives CIS to Seminoma(S), NonSem(NS) 4.0N 3.6N 2.7N.

Orchitis / Testis Atrophy due to viruses/chemicals/trauma/heat

p53 bcl2 mdm2 DNA repair.

Trauma / surgery cryptorch NS>S.
Drug addict HIV NS> S.
Azothiaprine imm-suppress NS>S

HIV(other) S>NS
Cryptorchidism no surgery S>NS

SEMEN ANALYSIS ON NORMAL MALES AND TGCT PATIENTS (Badenoch & Oliver 1990)

	Sperm count (x10⁶/ml)	<20 (x10⁶/ml)	≥20 (x10⁶/ml)
Normal Fertile **Male** (n=104)	84	11.5%	89%
Infertile (n=53)	10	68%	36%
Testis Tumour Stage1 Surv (n=16)	7.5	75%	25%
Mets pre-Chemo (n=24)	10	71%	29%
Mets post-Chemo (n=27)	7.0	70%	29%
Testis conserv chemo(n=10)	2.65	90%	10%

Fluctuating Pain & non-affected Testis size in GCT Patients (Oliver & Oliver Lancet 1996, 347:339-340)

Testis size	Adult Mumps (n=2)*	Fluctuating Testis Pain (n=12)*	Elevated FSH (>7iu/L) (n=21)*	Raised FSH + Testis Pain (n=7)*
Small (10ml) (n=13)	100%	58%	52%	86%
Intermediate (10-15ml) (n=13)		33%	33%	14%
Large (15ml) (n=12)		8%	14%	

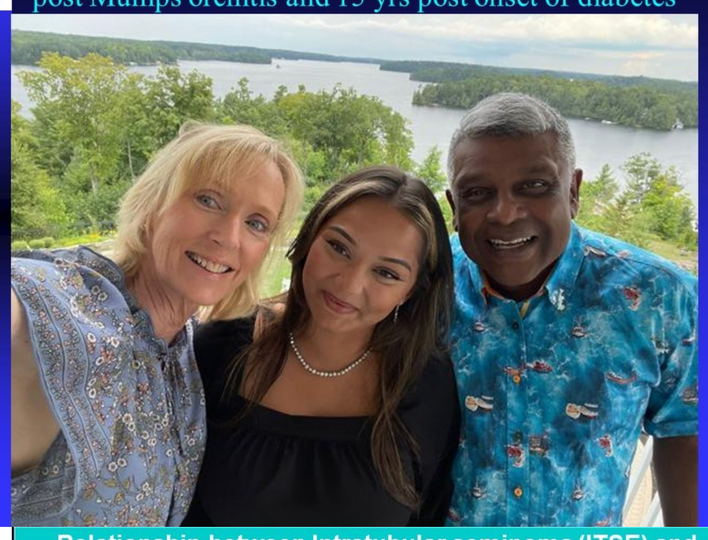
Pre-treat FSH & 2nd GCTs in TE19

(Oliver et al 2011 JCO 29:957-62)

Pre- treat FSH	No. 2nd GCT/No pts	5/10 yr event rate (95% CI)
>12 IU/L	*8/313	2.7%/3.2% (1.0%, 3.8%)
=<12 IU/L	*2/695	0.2%/0.4% (0.1%, 2.1%)

*The 5-year event rate is significantly higher in the FSH >12IU/L group than the group FSH =<12, HR 8.57 **p=0.001**

Family photo 20 yrs post successful IVF with sperm extraction from post bilateral TGCT orchidectomy 40 yrs post Mumps orchitis and 15 yrs post onset of diabetes



Epidemiologic Risk Factors and GCT Subtype (Coupland at Br J Cancer 1990;80:185a)

	No of cases	Seminoma	Significance
All cases	794	50%	-
Uni Cryptorch, Uncorr	12	67%	-
Uni Cryptorch, Corr	34	44%	0.16
No injury	759	51%	-
Testis/groin injury	35	34%	0.023
No STD	715	51%	-
History of STD	76	41%	0.018

IMMUNOSUPPRESSION AND GERM CELL CANCER PATHOLOGY AND STAGE

Histologic subtype	Number of cases	Seminoma(%)
AIDS Linked[a]	92	54
Post transplantation[b]	18	28
Spontaneous[b]	342	45
Clinical stage	**Number of cases**	**Stage 1(%)**
AIDS Linked	60	28
Post transplantion	18	28
Spontaneous	153	50

Relationship between Intratubular seminoma (ITSE) and Intratubular Non-seminoma/Embryonal carcinoma (ITEC) to final histological type of Germ Cell Tumour

ITSE	ITSE in Seminoma	ITSE in Seminoma & NS-TGCT	ITSE in NS-TGCT
Oesterhuis et al 2003(6)	27% (n=86)	44% (n=25)	17% (n=70)
Berney et al 2006 (7)	39% (n=33)	78% (n=9)	37% (n=30)
Van Eyben et al 2017 less above (8)	13% (n=94)	ND	15% (n=69)
ITEC			
Oesterhuis et al 2003	1.2% (n=86)	18% (n=22)	20% (n=70)
Berney et al 2004 (9)	3.7% (n=27)	25% (n=4)	37% (n=30)
Van Eyben et al 2017 less above	0% (n=62)	ND	7% (n=43)

Loss of total DNA and specific Chromosomes in TGCT clonal evolution

Modified from Oosterhuis et al *Eur J Urol* 1993;23:16-22.

	Number of cases	Median DNA Ploidy value	Centromeric Analysis*		
			#1	#2	#15
CIS areas next to seminoma	6	1.59	2.7	3.2	2.0
Seminoma Tumour	6	1.55	2.7	3.5	3.0
CIS areas next to nonseminoma	5	1.57	2.4	2.5	1.9
Nonseminoma	5	1.47	3.0	3.58	1.8

- number of centromeres identified by *in situ* hybridization of interphase nuclei.
- #1 #2 #15 = Chromosome1, chromosome2, Chromosome 15

Bacterial & Viral infection and fertility

The presence of increased neutrophils and macrophages in the absence of bacteria in aerobically cultured semen from infertile men is unexplained

Odour is well recognised to accompany bacterial vaginitis (BV) with anaerobic infection and is occasionally noted with semen samples

In three separate studies of Microbiota of semen there were reports of a trend for worse semen characteristics in those with anaerobe Prevotella and better characteristics in those with Lactobacillus as in Cervix Ca

It is now 46 yrs since Beard linked Testis atrophy and TGCT with Mumps

There are an increasing number of reports of poor semen parameters in men with HPV detectable on their sperm. Given synergy between BV and HPV in cervix cancer epidemiology, more attention need to be given to these two parameters in infertility studies, particularly given an HPV vaccination study from Italy achieved 40% pregnancy vs 14% in controls .

As semen analysis in TGCT report higher frequency of low sperm parameters in more advanced disease, study of aspirates of epididymis from testicular tumours at the time of Orchidectomy could show whether the ibetween HPV and anaerobes plays a role in this tumour progression

SUMMARY

The reduction of Gastric cancer seen after H. pylori treatment even in high risk families is evidence that paying attention to control of anaerobic microbiota could have as great an impact on oral and genitourinary malignancies.

Evidence that the anaerobic microbiota contributes to infertility problems and TGCT development is mostly from indirect evidence. However the emerging evidence for an increased role of HPV infection in infertility studies, taken with evidence for HPV and anaerobe interaction in oral, cervical, penile and prostatic cancer, increases interest into investigation of the relevance of HPV/anaerobe interaction in testis atrophy & TGCT development