Can I catch cancer?
(and the story of the Tasmanian Devils)
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Devil Facial Tumour Disease
First noted in 1996.

What is it?
• a fatal condition in Tasmanian devils, characterised by cancers around the mouth and head.
• a new disease that is restricted to Tasmanian devils
• animals usually die within a few months of the cancer becoming visible

Rapid declines in Devil numbers
• Populations in which DFTD has been observed for several years have declined by up to 95%
• confirmed across more than 60% of the State.
• Still spreading
“Devils extinct in 25-30 years”

What is it and how is it spread?

- Histology and genetic sequencing showed it to be a neurosarcoma derived from Schwann cells.
  - Poorly differentiated, aggressive carcinoma
  - Similar in all the animals
Transmission between animals

- DFTD tends to arise in the lips, oral mucosa, or the face of Tasmanian Devils
- Frequent “jaw wrestling”
- DFTD may be spread by biting

How did it spread

- Clearly transmissible
- Most known transmissible cancers are spread by viruses -15% of all cancers
  - HPV - cervical carcinoma
  - HepB - hepatocellular carcinoma
  - EBV - Burkitts lymphoma and nasopharangeal carcinoma
  - HHV-8 - Kaposi’s sarcoma
  - Polyoma virus - Merkel Cell carcinoma virus

But this cancer is different

- It is a direct implant from one animal to the other by cancer cells
- Only one of three cancers known to do this

RNA viruses
- Hep C virus - hepatocellular carcinoma
- HLTV-1 - adult t cell leukemia/lymphoma

Bacterial infections
- H. pylori - gastric carcinoma
- C. psitticial - ocular adnexal lymphomas
What are the others?

- canine transmissible venereal tumour
  - A single malignant clone of CTVT cells has colonized dogs worldwide, originating 6000 years ago, it represents the oldest known malignant cell line in continuous propagation
- contagious reticulum cell sarcoma of the Syrian hamster
  - transmitted from one Syrian hamster to another by means of the bite of the mosquito Aedes aegypti

Evidence that the cancer is transmitted

- The karyotype of the cancer from different animals is exactly the same.
  - Normal devils have 14 chromosomes, DFTD has 13.
- Chromosomal abnormalities in the host are not seen in the cancer e.g. a ring chromosome 5 present in one animal was absent in the cancer

a. Normal karyotype for a male Tasmanian devil (14 chromosomes, including XY). b. Karyotype of cancer cells found in each of the facial tumours of all 11 animals studied (13 chromosomes, with no sex chromosomes, no chromosome-2 pair and only one chromosome-6; the long arm of one chromosome 1 was deleted; four additional marker chromosomes were present (M1–M4).
Why aren't cancers normally transmissible

- The host immune system recognises the cells as foreign and destroys them.

Major histocompatibility complex

- a large genomic region or gene family found in most vertebrates
- MHC molecules display fragments of processed proteins from foreign cells on the cell surface.
- The presented proteins activate an immune response through cytotoxic and helper T cells

HLA

- The best-known genes in the MHC region are the subset that encodes antigen-presenting proteins on the cell surface.
- In humans, these genes are referred to as human leukocyte antigen (HLA) genes

HLA

- The set of alleles that is present in each chromosome is called MHC haplotype.
- In humans, each HLA allele is named with a number. For instance, for a given individual, his haplotype might be HLA-A2, HLA-B5, HLA-DR3, etc...
- Each heterozygous individual will have two MHC haplotypes, one in each chromosome (one of paternal origin and the other of maternal origin). Both are expressed.
The MHC genes are highly polymorphic; this means that there are many different alleles in the different individuals inside a population.

No two individuals exist with exactly the same set of MHC genes and molecules, with the exception of identical twins.

MHC allows us to reject foreign tissue

- In a transplant (an organ transplantation or stem cells transplantation), MHC molecules work as antigens.
- They can initiate an immune response by activating T cells, which can directly kill cells (cytotoxic) or activate other cells to attack (helper).
- MHC molecules recognition in cells from another individual is one of the most intense immune responses currently known.

So why does this foreign tissue grow in Tasmanian devils?

- The devils have a low genetic diversity
- They are more closely related than the most inbred of dogs
- 30% of them have the same MHC as the tumour - they are “identical twins” by MHC standards
- 70% are close enough to not mount an immune response to DFTD

Low genetic diversity

- Once widespread across Australia they became a remnant population on Tasmania about 3000 years ago.
- In modern history there have been population crashes due to disease, trapping and poisoning.
- The low genetic diversity is due to the founder effect
- A human example is in Iceland where 25% of the population carry the BRCA gene.
Difference between DFTD and CTVT

- Although capable of metastasizing, CTVT often does not require treatment, as spontaneous regression is the general rule.
- In most cases, the dog's immune system eventually reacts to the allograft and clears it, rendering the dog immune to future challenges.

- Although CTVT is ultimately rejected, it has some fascinating properties that have allowed it to persist and be transmitted for so many generations.
- It down regulates its MHC I expression, thereby reducing its visibility to the host's immune system.
- This clever downregulation (rather than complete absence) allows it to not only escape T-cell-mediated immunity (which would occur if MHC I were fully expressed) but also natural killer cells (which would eradicate the cells were they completely devoid of MHC I).

Have there been cases of humans transmitting cancers to one another?

- A healthy 19-year-old woman, employed in a laboratory outside the National Institutes of Health, who had no clinical history to suggest immune deficiency. While she was injecting mice, her left hand was accidentally punctured by a needle that had previously been used to draw up a human adenocarcinoma cell line.
- 2 weeks later a nodule appeared at the site.
- When excised it was histologically identical to the adenocarcinoma with the same HLA type as the tumour and different to the lab worker.

The case of the surgeon

- A 32-year-old man underwent emergency surgery to remove a malignant fibrous histiocytoma from his abdomen and died shortly thereafter of postoperative complications. During the operation the 53-year-old surgeon injured the palm of his left hand while placing a drain. The lesion was immediately disinfected and dressed.
• Five months later, the surgeon consulted a hand specialist because of a hard, circumscribed, tumor-like swelling, 3.0 cm (1.2 in.) in diameter, in his left palm at the base of the middle finger, where he had been injured during the operation. An extensive examination, including laboratory tests, did not reveal any signs of immune deficiency. The tumor was completely excised. Histologic examination revealed that it was a malignant fibrous histiocytoma.

• Two years later, the surgeon’s condition was good, and there was no evidence of recurrence or metastasis of the tumor.

• Histologic analysis of tumour tissues from the surgeon and the patient revealed that they were morphologically identical.

• In the periphery of the surgeon’s tumor, there was intense inflammation, with an infiltrate consisting mainly of lymphocytes and macrophages and few plasma cells.

• Analysis of short tandem-repeat polymorphisms, and sequence-based typing of HLA genes determined the genetic origin of the sarcoma to be a chimera between the patient and surgeon.

A case of transplanted melanoma from a daughter to her elderly mother

• “The original tumor was a melanoma which first appeared on the midback in a 50-year-old white female in 1958. The lesion was treated by wide local excision; no further treatment was given and in the summer of 1961 diffuse metastasis appeared.”

• “The tumor was transplanted into hamsters for further study but it could not be carried beyond a few generations. The patient’s family had familiarized themselves with some of the studies being done in the laboratory and, as the patient became terminal, her mother volunteered to have the tumor transplanted into herself.”
• “It was felt at that time that there was probably no risk from the transplanted tumor but the mother was informed that the tumor might grow and metastasize.
• The mother was 80 years old but physiologically was 10 to 15 years younger and was generally in good health.
• On the day of transplantation she was in good health. The blood type of the mother was A,CDE (positive): the daughters blood type was AzcDE (positive).

• The tumor was transplanted on August 15, 1961. Under local anesthesia a small piece, less than 0.5 cm. in diameter, of subcutaneous melanoma was removed from the daughter and transplanted as a single piece into the right rectus muscle of the mother.
• The next day the daughter suddenly expired from generalized peritonitis following perforation of small bowel.
• On the twenty-second post-transplantation day the recipient complained of a pulling sensation in the abdominal wall.

• A biopsy was taken and melanoma was demonstrated in the rectus muscle. On the twenty-fourth day a wide excision of the right upper quadrant was done; skin, subcutaneous fat and a large piece of rectus fascia and muscle, as well as peritoneum, were removed.
• The patient was then well until the sixty-fifth post-transplantation day when she began to complain of constipation and pain in the abdominal wall.
• On the eighty-sixth post-transplantation day a small incision was made in the right upper quadrant and a plaque of tumor was found growing over the loops of bowel.

• The patient’s general condition began to deteriorate and she developed symptoms of high grade partial bowel obstruction. The patient appeared terminal.
• Unexplainedly her condition slowly began to improve. She gained weight and strength; she became ambulatory and returned to nearly normal activity.
• In October of 1962 she fell and fractured 3 ribs, following which she had constant chest pain.
• She was re-admitted to the hospital on November 7, 1962 and her clinical course was progressively down-hill until she expired on November 10, 1962, 451 days after the transplant had been made.
• Post-mortem examination demonstrated diffuse metastasis from the melanoma, including lungs, ribs, diaphragm, pericardium, skin and mediastinal lymph nodes, whose histological appearance is indistinguishable from that of the original tumor in the daughter.


In 1958 there was an experimental series where volunteers were transplanted with cancer cells

• “In brief, normal human recipients responded to implanted human cancer cells with a marked inflammatory response…..In striking contrast however those recipients that had advanced cancer showed little or nor acute inflammatory response and the implanted cells grew progressively for a period of three weeks or more before regression started and some individuals failed to reject implanted cancer cells over periods of observation between six weeks and 6 months.”


Special circumstances

• About 1/1000 women develop a malignancy during pregnancy, and in rare cases, mother-to-fetus transmission of melanoma, lymphoma, leukemias, and carcinomas have been reported as well as fetus-to-fetus transmission in twins.

• Although exceedingly rare, 0.04% of organ transplant recipients contract cancer from the donor organ (mostly melanomas) and haematologic malignancies have been observed in about 0.06% of hematopoietic stem cell transplants

• about one third of recipients of organs from donors with some form of cancer at the time of donation eventually developed the same malignancy as in the donor.

• The absence of cancer in the rest is most likely due to the host’s rejection of foreign malignant clones.

• In cases in which cancer does develop following transplantation of an organ from a donor with cancer, the malignant process may regress after the graft has been removed and immunosuppression discontinued
Most cases describe are from the 1970’s and 80’s. The most recent is from 2003—a kidney and liver were transplanted from a donor who was found to harbour pancreatic adenocarcinoma. The liver recipient was re-transplanted within 24 hours, whereas the kidney recipient opted not to undergo removal of the transplanted organ; the liver recipient died with metastatic pancreatic adenocarcinoma 15 months after transplantation.


Sometimes incidental renal cell carcinoma is found at renal transplant. If these can be excised at the time of the operation then the remainder of the organ can be transplanted with little risk of the cancer recurring.

Kaposi’s sarcoma in transplant patients

- organ transplantation carries a 1 out of 200 risk of Kaposi sarcoma
- the disease could originate directly from donated neoplastic cells or as a result of reactivation of the Kaposi sarcoma–associated herpesvirus KSHV
- Kaposi sarcoma in 5 of 8 renal transplant patients had genetic or antigenic markers of their matched donors, suggesting that they were transplanted malignancies (KSHV)


Can you catch cancer?

- Only in special circumstances
  - Large tumour inoculum
  - Matching MHC
  - Immunosuppressed