

SHORT REPORT

Unexpected medical coincidences require systematic and careful strategies: an example

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In a cohort of 14 children with identical cardiac xenografts, two boys developed acute myeloid leukaemia 11 and 16 months respectively after the operation. A dedicated working group designed a scheme intending to take care of all aspects of the situation. This article focuses on preferred strategies towards patients, relatives, government, and the media. We did not find any substantial evidence supporting the association between bovine xenografts and two cases of acute myeloid leukaemia.

Occasionally, in relation to implementation of new medical approaches, unexpected and challenging observations emerge requiring immediate reactions from the health service. At our institution, we recently observed acute myeloid leukaemia (AML) in two children with identical cardiac xenografts, coincidences regarded as both surprising and alarming. This article describes how the situation was handled, and focuses on our preferred strategies towards patients, relatives, government, and the media.

Xenotransplantation is defined as the transplantation into humans of tissues or cells of animal origin for therapeutic purposes.¹ Xenografts for correction of congenital heart defects have been used in the past two decades, mostly because of shortage of proper sized and more suitable homografts.² Medical use of animal tissue for human purposes is associated with a number of possible dangers,³ for instance rejection,⁴ viral infections,⁵ prion diseases,⁶ and related subjects. The observation of AML in two children with cardiac xenografts underlines the necessity of caution in dealing with xenografts, but most importantly the need for established systems, within the health service, to take care of unexpected and startling events.

THE MEDICAL COINCIDENCES

At the National Hospital in Oslo, from February 2000 to February 2001, 14 children with complex congenital heart diseases received identical bovine cardiac xenografts (Contegra, VenPro Corporation, CA). The children were all under the age of 4 years; nine were infants. The bovine conduits tended to cause both undesirable stenosis at the distal anastomosis and dilatation, resulting in discontinuation of further use. Among the 14 children with bovine conduits, two children developed AML 16 and 11 months respectively after the operation. Table 1 briefly describes the cases and their leukaemias.

MANAGEMENT

The occurrence of two cases of AML in a small cohort of children with identical xenografts was of concern, and urgent reactions from the responsible health institution were needed. The circumstances had the potential of becoming a public health concern, and establishment of a working group consisting of representatives of all implicated departments had high priority. This group designed a scheme intending to take care of all aspects of the situation. We decided to inform all involved parties, and giving information to all the parents in the cohort was most pressing. The parents had to be informed by a doctor, with whom they had a confidential relationship, before the event was presented in the media. The government, represented by the county medical officer, required information at an early stage. Figure 1 illustrates how we defined the different parties entitled to direct information. At the same time, we searched for similar cases and further information about the topic.

The parents of the affected boys were the first to be informed about our observations. They approved of informing the parents of children with similar bovine xenografts (n = 12). A paediatric cardiologist, a paediatric oncologist, and a dedicated nurse had individual consultations with the other children and their parents. The peripheral haematology

Table 1 Characteristic features of the affected children and their leukaemias

	Case 1	Case 2
Congenital heart defects	Extreme tetralogy of Fallot	Truncus arteriosus communis, interrupted aortic arch, VSD
Other birth defects	Atresia of oesophagus, ureteropelvic stenosis	None
Location of the leukaemia	Bone marrow	Bone marrow
Bone marrow infiltration	85%	95%
Immunophenotyping	CD 45, MPO, HLA-DR, CD 34, CD 117, CD 13, CD 33	CD 45, CD 33, CD 64, CD 11c, HLA-DR, CD 38, CD 56
Cytogenetics	Normal karyotype	t(9;11)
FAB classification	M2	M4/5
Treatment protocol and response	NOPHO-AML 1993, CR in 9 months, dead 11 months from diagnosis	NOPHO-AML 1993, CCR

FAB, French-American-British classification; NOPHO, Nordic Organisation of Paediatric Haematology and Oncology; AML, acute myeloid leukaemia; CR, complete remission; CCR, continuous complete remission.

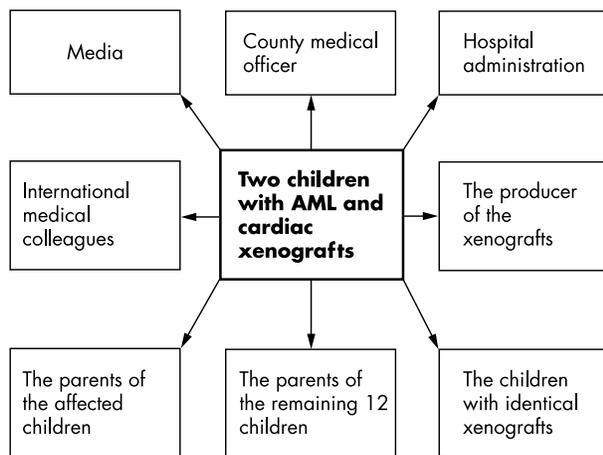


Figure 1 The spectrum of involved parties entitled to information.

of these children was analysed, and general information was given to close relatives.

The information was leaked to a television channel which intended to broadcast the news immediately. However, a meeting with the television channel clarified the situation and postponed broadcasting, and they respected the need for all the families to receive information before the events became a media case. A few weeks later, another television channel referred to our two patients in a programme about xenotransplantation. Their message about the current circumstances was correct and enlightening, probably as a result of constructive talks with our group.

Simultaneously, we performed extensive searches to look for similar cases worldwide. International colleagues were consulted directly and by the use of cardiac websites. The manufacturer of the bovine conduits was informed about our observations, and they assured us that the xenografts were safe. Finally, the county medical officer was given the complete story, and a detailed description of how we had dealt with the challenging issue.

The peripheral haematology of the remaining children in the cohort was normal, with no suggestion of leukaemia or other haematological disease. International enquiries did not reveal any similar cases. The affected children had two different types of AML with no similar features (table 1). Thus, we considered the observation of AML in two children with identical xenografts as coincidental.

DISCUSSION

The most important conclusion from our story is that determined strategies for management of unexpected events are for the benefit of all. Every health institution profits from established systems to take care of alarming events, and the system must preferably be instituted before an event occurs. Another significant conclusion is that giving open minded information at an early stage to all involved parts is essential for an acceptable result. The famous Bristol case, in which three senior doctors were found guilty of serious professional misconduct because they withheld information about correct death risks,^{7,8} shows the importance of appropriate information at an early stage. Information must be individualised, but all involved parties have to be informed fully about possible critical side events related to medical treatment.

In our department, some of the paediatricians were reluctant to add extra anxiety to the families without knowing the extent of our observations. However, even if the information caused the parents extra concern, they were all grateful and preferred to know about our observations. The parents were pleased to be involved at an early phase, and expressed gratitude for being treated in a respectful and including manner.

The media was eager to broadcast the incidents immediately, and we think the event would have been presented in a more sensational manner without direct consultations between the working group and the television channels. But the most important consequence of the cooperation with the media was postponement of broadcasting, allowing us to inform the parents before it became a media case. Meetings with the media were successful, and in our opinion, they presented the cases subsequently in a proper and thoughtful way. We do think biased information was avoided as a result of exchange of information between the two parties, and we recommend other health institutions to cooperate with the press in similar cases.

International quality of health research shows that the information infrastructure is one of the main components considered when patients are evaluating health services.⁹ About one half of all patients attended to a hospital have complaints, and complaints about information procedures are most frequent.¹⁰ The importance of information was confirmed in a similar study on parents of hospitalised children.¹¹ Communication is an essential feature of modern medicine.

Both boys described in this article had congenital malformations, and studies have shown that children with malformations have increased risk of various malignancies.¹² Even minor anomalies are associated with a higher frequency of malignancies.¹³ A study from the Children's Cancer group reported AML more often among children with congenital heart defects (odds ratio 2.07) than among children without malformations; children with Down's syndrome were at a particularly high risk (odds ratio 76.8).¹⁴ There are convincing indications of an increased susceptibility to cancer for children with congenital defects, and, at the moment, no substantial evidence of an association between cancer and bovine xenografts.

CONCLUSION

Surprising and unwanted events occur in medicine, and every health institution should be prepared to handle such situations. Two cases of AML in a cohort of 14 children with equal xenografts of bovine origin challenged our institution. A comprehensive search failed to find any clear relation between cardiac xenografts and cancer. Nevertheless, alarming events must be dealt with in a systematic and informative manner to avoid concealment of potential important medical relationships and to take care of all involved parties. Our institution made an extensive effort to handle the cases in a responsible manner, and we do believe that our immediate informative actions towards the involved parents and our open minded attitude regarding the press limited the challenges of the situation and were for the benefit of all parties.

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