THERAPEUTIC CHALLENGE

Cancer of unknown primary

The role of genetic signatures and targeted therapy. By Dr James Mackay, Dr Andrea Pithers and John Symons

CASE STUDY

Jo Symons was diagnosed with metastatic cancer in January 2006. She died from A-CUP eight months later, aged 46. She had seen her GP twice towards the end of 2005, with a persistent cough, lower back pain, cervical lymphadenopathy and general malaise. On a third visit, Jo was seen by a different GP, who immediately referred her to a consultant.

Immunohistochemistry analysis of the core biopsy of Jo's lymph node offered a diagnosis of metastatic cancer with a suggestion of ovarian cancer. Jo was then referred to a gynaecologist, who was adamant it was not ovarian cancer.

Jo was referred to a medical oncologist who repeated a conventional range of basic tests, as well as PET and CT scanning. Still there was no evidence of the primary. After reviewing the data and recognising Jo's age, fitness and history, the oncologist decided to treat her for breast cancer.

The chemotherapy regimens had little impact. Gene expression profiling was then tried. A sample of Jo's original biopsy was investigated using a CUP-print service. Pancreatic cancer was proposed, using a 'nearest neighbour' strategy. In a meeting with the oncologist to review treatment, the decision was made to treat on this basis.

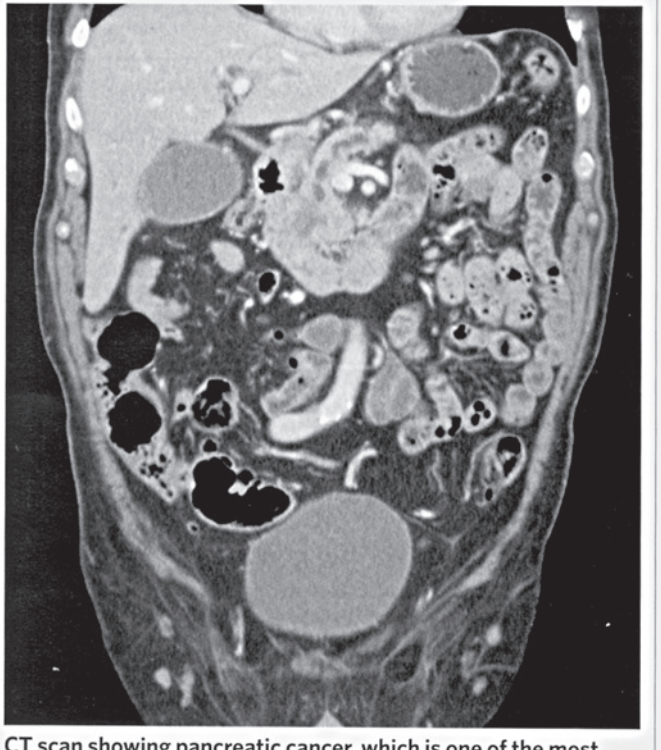
No postmortem was conducted, so it is impossible to validate the molecular identification of Jo's tumour. It did, however, change patient management and may have extended Jo's life. In a way, pancreatic cancer made more sense of the symptoms and gave some reassurance that treatment was being directed at a known cancer, rather than a wide range of anatomical possibilities.

This is a personal account of Jo Symons' experience, written by her husband, John Symons

All oncology health professionals will have experienced the difficulties of treating patients who present with metastatic cancer, but in whom no primary site of origin can be identified. Management of these patients presents unique challenges. In this clinical situation, the diagnosis is known as cancer of unknown primary (CUP).[1]

It is known that 90 per cent of CUPs are adenocarcinomas or poorly differentiated carcinomas, known as adenocarcinoma of unknown primary (A-CUP), 5 per cent are squamous carcinomas and 5 per cent are neuroendocrine carcinomas.[2] Common primary sites for adenocarcinomas are lung, pancreas, breast, prostate, stomach, liver and colon. CUP accounts for approximately 3–5 per cent of all new cancers. More than 10,000 cases are diagnosed in the UK each year.

The clinical presentation is extremely variable and depends on the extent and type of organ involvement. Most patients present with multiple lesions in multiple visceral sites, with the most common being lung, bone, lymph nodes and liver. Most patients have the constitutional symptoms of malaise, weakness, fatigue and weight loss seen in many advanced stage cancers. The diagnosis is made after the finding of a biopsy-proven malignancy, when a detailed history and physical examination are unrevealing and further appropriate investigations fail to pinpoint the site of origin (figure 1, page 10).



DR P MARAZZI/SPL

CT scan showing pancreatic cancer, which is one of the most common primary sites for adenocarcinomas

PROGNOSIS

The median survival ranges from 11 weeks to 11 months. The reported five-year overall survival rate is about 11 per cent.[3] This may be because a small minority of patients diagnosed with CUP do unexpectedly well, or because some are misdiagnosed with CUP because of inadequate diagnostic work-up.

MULTIPLE GENETIC SEQUENCES

Examination of the activity of multiple genetic sequences reveals genetic signatures that are highly tissue specific. One signature is found in lung tissue, a different one in liver tissue. These signatures are specific and repeatable, and therefore could represent an accurate method for determining the tissue of origin of an unknown tissue sample. However, when that tissue sample has been derived from a cancer, it is possible that in the process of carcinogenesis, the unique properties defining the tissue of origin are lost. If that were the case, these genetic signatures would be unhelpful. In reality, it appears that the tissue-specific properties are robust, so even a very advanced and highly aggressive cancer retains a genetic signature that allows identification of the tissue from which it originated.

TARGETED THERAPY

Traditionally, patients with CUP have been treated with a chemotherapy regimen suitable for the most likely primary site, which was often nothing better than a wild guess. More recently, however, healthcare institutions have adopted a more standard chemotherapy regimen to treat all patients once the diagnosis of

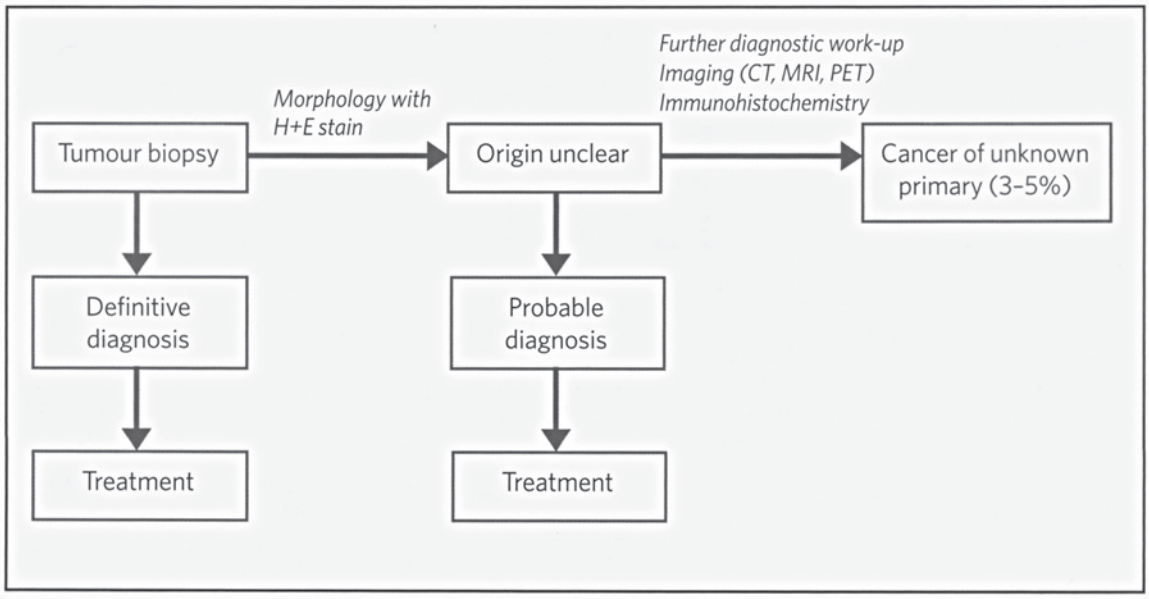


Figure 1: Diagnostic work-up

CUP has been made. Even with this approach, the prognosis of a patient with CUP, with multiple organ involvement and poor performance status, is grave; the median survival is only three to four months. The usual chemotherapy regimen used to treat a patient diagnosed with CUP involves the combination of a platinum compound and a taxane. This combination gives a response rate of about 12–26 per cent and a median survival of five to seven months.

The recent development of targeted therapy regimens (see box 1) offers the possibility that accurate identification of the tissue from which the cancer originated may have therapeutic benefit. For example, if a tumour sample from a patient diagnosed with CUP is shown to be a colorectal cancer, that patient would be treated with cetuximab, rather than the platinum/taxane combination.[4]

Theoretically, clinicians would expect that using targeted therapy to treat a significant percentage of patients formerly diagnosed with CUP would improve outcome and toxicity. This would apply at least to those patients in whom a definitive tissue diagnosis led to the prescription of targeted therapy. In patients in whom a definitive diagnosis led only to a slight change in conventional chemotherapy, a much less significant impact would be expected.

FUTURE RESEARCH DIRECTIONS

If CUP is a distinct biological entity, rather than a heterogeneous grouping of various cancers in which the primary has been difficult to identify, the picture changes. It is possible that CUP represents a group of cancers that share a particularly undifferentiated appearance and very aggressive behaviour. In that case, it is possible that in these particularly aggressive cancers, even targeted therapy would not be effective. A reduction in overall toxicity in the targeted therapy group would therefore be seen, but no impact on mortality.

This is now the crucial question in the care of patients presenting with CUP. Does identification of the tissue of origin and the use of more targeted therapies improve the median survival in this group? It is known that a small percentage of patients in the group do well, with a five-year survival rate of 11 per cent. Further primary clinical research in this patient group is urgently needed. ■

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BOX 1: TARGETED THERAPIES FOR CANCER TYPES

Tissue type	Therapy
Non-Hodgkin's lymphoma	Rituximab, ibritumomab tiuxetan
Colorectal	Cetuximab, panitumumab, bevacizumab
Hepatocellular	Sorafenib
Renal	Sorafenib, sunitinib, tesirolimus
Prostate	Antiandrogens
Thyroid	Radio-iodine
Sarcoma	Imatinib, sunitinib (GIST)
Breast	Trastuzumab, lapatinib, antiestrogens
Non-small cell lung	Bevacizumab, gefitinib, erlotinib

THE CANCER OF UNKNOWN PRIMARY FOUNDATION

Following the death of Jo Symons, her friends established the Cancer of Unknown Primary Foundation. This foundation, also known as Jo's friends, was established to provide information and support to CUP patients and their families. The foundation also encourages research into CUP.

The first international conference on CUP, drawing in experts from around the world, will be held by the Cancer of Unknown Primary Foundation in London on 15 October, at the Royal College of Obstetricians and Gynaecologists. For further information, please visit **www.cupfoundjo.org**

Competing interests: Dr James Mackay and Dr Andrea Pithers are founder directors of Trinity Health Innovations

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● *Cervical lymphadenopathy from unknown primary, page 34*