Bone Cancer – A rare complication of Paget’s Disease

The following pages contain discussion regarding a type of bone cancer (osteosarcoma) that is a very rare complication of Paget’s disease. We look at this firstly from a medical point of view and then from the very personal experience of Mrs Norma Reid who lost her husband to this devastating condition.

Paget’s Disease of Bone-associated Osteosarcoma: Molecular Basis, Signs & Symptoms, Treatment and Research

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INTRODUCTION

Paget’s associated osteosarcoma is a type of bone cancer that is a very rare complication of Paget’s Disease of Bone. In less than 1:1,000 patients, Paget’s disease can trigger a change in one of the main types of bone cell known as an osteoblast, turning the cell abnormal and becoming cancer like (malignant). Bone cancer resulting from these changes in osteoblasts is called ‘osteosarcoma’. This type of cancer is most often found in children and young adults. While Paget’s patients are at risk of developing osteosarcoma, it is important to realise it is extremely rare. Modern treatments for Paget’s disease are believed to inhibit the development of Paget’s associated osteosarcoma.

In this article, we explain the molecular basis of osteosarcoma, discuss identification of patients at risk, describe the signs and symptoms to look out for, then outline possible treatments for osteosarcoma. We also explore the current direction of research into the causes and diagnosis of this rare complication.

MOLECULAR BASIS

At an individual level, ‘cancer’ is rare. It is a genetic event where a cell has typically undergone alterations within its DNA, causing a downward spiral of uncontrolled growth. To put into perspective, our DNA naturally changes every eight seconds. That equates to almost eleven thousand alterations every day. For 66% of the UK population, cancer will never happen. The human body has remarkable systems in place to ensure DNA damage is successfully repaired. There are many different types of cancer and bone cancer is considered a rare cancer. Therefore Paget’s associated osteosarcoma is a rare complication of the second commonest metabolic bone disease in the UK.
The increased speed of bone remodelling in Paget’s disease can increase the number of alterations to the DNA of osteoblasts, the bone cells responsible for making new bone. Even in a disorder such as Paget’s disease, our bodies have mechanisms in place to withstand the increased damage to our DNA. It is only in less than 1:1,000 cases where a cancerous osteoblast can slip through the net and evade our defences. Drugs used to treat Paget’s disease, such as Zoledronate, work by slowing down the rate of bone remodelling. This also has the effect of reducing the number of alterations that occur in osteoblasts compared to that of untreated Paget’s disease.

One of the major goals in cancer research today is to identify the alterations that cause different types of cancer. That way, doctors and scientists can predict how and when a cancer might occur. At present, the exact alterations that cause Paget’s associated osteosarcoma are unknown. It is therefore vital to identify the individuals most at risk of developing osteosarcoma and make sure all patients are aware of the early signs of possible changes in the bone.

PATIENTS AT RISK

Paget’s Disease of Bone can arise due to alterations in one or more genes. Some of these genes have a different impact on the severity of the disease. Alterations to the SQSTM1 gene have been linked to an earlier onset of Paget’s disease, an increase in disease severity and an increase in chronic bone pain. It has been noted that patients carrying the SQSTM1 gene are most at risk of developing Paget’s associated osteosarcoma. However, this does not mean to say that other patients with a different set of genes cannot develop bone cancer. It also doesn’t mean that all SQSTM1 positive patients will develop bone cancer. All patients should be regularly monitored and made aware of the early signs of Paget’s associated osteosarcoma. As with all cases of cancer, early diagnosis is key to a good outcome.

SIGNS & SYMPTOMS

Bone cancers such as osteosarcoma are typically hard to spot because their signs are usually attributed to other factors, such as an accidental bump or knock. A key contrast between a slight knock and Paget’s associated osteosarcoma is that bone cancer pain will progressively get worse. Some patients can experience trouble sleeping because of the increased pain. This is readily noticeable in comparison to any ‘normal bone pain’ patients suffer due to Paget’s disease. It is imperative that any new pain or significant change in pain is reported to a doctor. Other symptoms can include a significant change in bone shape with swelling in the bone usually close to the area where the pain is increasing.

The blood test, serum alkaline phosphatase, which can be elevated in Paget’s disease, may increase further and quite rapidly with the onset of Paget’s associated osteosarcoma. X ray images may reveal a change in bone structure, a vague tumour mass extending beyond the bone, destruction to the surrounding bone and fracture (Figure 1b). A Computerised Tomography Scan (CT), Magnetic Resonance Imaging (MRI) or Positron Emission Tomography scan (PET) may sometimes be helpful in identifying the presence of osteosarcoma. Further confirmation that Paget’s disease has resulted in osteosarcoma can be made by obtaining a sample (biopsy) of the affected bone. A small needle is used to extract some of the abnormal tissue and a specialist pathologist will look at the cells under a microscope to confirm whether the osteoblasts have become cancerous. The tell-tale signs at this stage are cells that are much larger than normal, containing ‘messy’ looking DNA that are secreting an immature form of bone (Figure 2b).
If it is found that osteosarcoma is present, it is important to undergo a medical examination called ‘staging’. This is to determine if the cancer has spread, or ‘metastasised’, elsewhere around the body. The tests commonly used are chest X rays, lung tomograms, CT and bone scans. There are four possible outcomes in staging:

| Stage 1 | The osteosarcoma is fairly small in size and it is ‘localised’ – meaning it hasn’t spread from the original site. |
| Stage 2 | The osteosarcoma is larger in size than Stage 1 but still hasn’t spread to other parts of the body. Some cancer cells may be getting closer to the lymph nodes. |
| Stage 3 | The osteosarcoma tumour is now much larger and has started to invade the nearby healthy tissue. Some cancer cells may have entered the lymph nodes. |
| Stage 4 | The osteosarcoma has spread to other parts of the body and further osteosarcoma tumours have arisen in other organs. This is called ‘secondary’ or ‘metastatic’ cancer. |

**TREATMENT**

There are less treatments available for Paget’s associated osteosarcoma than there are for childhood osteosarcoma. Long-standing Paget’s disease results in the bone developing an increased network of blood vessels. This makes localised surgical removal of the tumour much more difficult, as there is an increased risk of cancer cells leaking into the bloodstream and then spreading around the body. This would result in the tumour growing in other tissues (metastatic disease). To avoid this, surgeons may have to perform a limb-sparing procedure. This is when a surgeon removes the tumour as well as surrounding healthy tissue and bone to ensure there is no cancer left behind. The affected limb is reconstructed using prosthetic devices and bone grafts. In some cases it may be required to perform more extensive surgery, which could mean limb amputation as a life-saving procedure.

Surgery is often followed by further treatment using one or more anti-cancer drugs as ‘chemotherapy’. This is to ensure that any cancer cells left behind are destroyed as well as preventing relapse of the disease. If the osteosarcoma is detected early on, it is possible to avoid drastic surgery and start with chemotherapy. In all cases, chemotherapy is delivered in ‘cycles’ – a couple of days spent in hospital receiving treatment followed by a few weeks of rest. Two drugs may be given called cisplatin and doxorubicin, which work by damaging the DNA of cancer cells so they cannot function and as a result the cells die. Just before the end of one treatment cycle, a drug called methotrexate may be prescribed which works by blocking the cancer cells from multiplying.

Common side effects of treating Paget’s associated osteosarcoma with chemotherapy are similar to that of many cancer treatments; which can include nausea, sickness, diarrhoea, tiredness and hair loss. Each patient responds differently to chemotherapy, some patients will experience the side effects whereas others may not. Due to the age of a typical Paget’s associated osteosarcoma patient, the decision may be taken to give palliative radiation therapy. The purpose of radiation here is to try to slow the growth of the tumour rather than completely removing the cancer.
FUTURE RESEARCH

A recurring theme of this article is that Paget’s associated osteosarcoma is incredibly rare. As a result, there has been a limited amount of research performed and only a small number of research projects currently taking place. A key question for researchers is how the SQSTM1 gene may play a role in the development of osteosarcoma. Out of the several genes involved in Paget’s Disease of Bone, why is this one in particular an increased risk factor? Perhaps it is not the gene itself, but the regulation of the gene by external mechanisms. Genetic studies on tumour samples or cells in a laboratory may provide clues as to how this happens.

Another line of research that is of particular interest to our laboratory, is the identification of simple biomarkers that can be used to accurately identify when a patient has or is developing osteosarcoma. As with other bone cancers, it can take some time for the cancer to develop and cause symptoms. That can make osteosarcoma very difficult and expensive to diagnose. Our laboratory has been studying molecules found in the bloodstream that may be detected by a simple fingerstick blood spot test that could be taken by the patient in their own home. The sample can then be sent to the laboratory to allow regular monitoring and possible earlier diagnosis. If this method turns out to be readily reproducible, reliable, cheap and easy to automate it could well be introduced in the future to help early diagnosis of osteosarcoma. There is also the possibility of introducing treatment at a time when it would have a greater efficacy.

SUMMARY

- Paget’s associated osteosarcoma is a bone cancer that occurs in less than 1:1,000 of patients with Paget’s Disease of Bone.
- Drugs used to treat Paget’s disease, such as Zoledronate, may reduce the risk of bone cancer development.
- Symptoms of bone cancer include progressive pain that increases at night and sudden swelling around the affected bone.
- Chemotherapy is used to treat most bone cancer.
- Radical surgery may also be required.
- Research into Paget’s-associated osteosarcoma is trying to answer how the SQSTM1 gene may be involved and if molecules in the bloodstream may act as a quicker and cheaper route to diagnosis.
Figure 1a

X-ray showing Paget’s disease of bone in the head of femur. The bone is sparse and almost see-through in some parts.

Figure 1b

X-ray from the same patient showing osteosarcoma development in the femur. The bone appears thickened with structural changes. Evidence of a vague tumour mass blurs the outline of the bone.
Figure 2a
Photomicrograph of normal bone. The cells (purple dots) are small in size and number, with surrounding healthy bone (in pink).

Figure 2b
Photomicrograph of a biopsy sample. The DNA of the cells (dark purple) is messy and irregular in shape, instead of being in neat circles. There are many oval shaped cells compared to the amount of bone (light pink staining). This is a clear example of where osteosarcoma has arisen in Paget’s bone.

Figures 1a, 1b, 2b - Images reproduced from: Osteosarcoma arising on a background of Paget’s disease report of an unusual case, A Qureshi, KF Zahid, SI Ibrahim, I Burney, 2013, with permission from BMJ Publishing Group Ltd.

Figure 2a – Taken by Professor Richard Ball at the Norfolk and Norwich University Hospital.
Remembering Allan

Allan Reid was born in Glasgow in 1957. At the age of 49, he was diagnosed with Paget’s disease. Last year Allan died, aged 57, from Paget’s – associated osteosarcoma, a type of bone cancer that is a very rare complication of Paget’s disease. His wife, Norma shares below their traumatic experience and explains how his family and friends are fundraising to ensure something positive comes out of Allan’s death.

For most of our married life Allan and I lived in Newton Mearns, a suburb in southern Glasgow. We had been married almost 35 years when Allan died. Our two daughters live close by: Jill with her fiancé Steven; and Pam with her husband Iain, and their daughter Sophie who was born last April. Allan was so proud to become a Granpa and his 80 year old mother, Margaret, a Great Grandma. Sophie was only 3 months and 3 weeks old when her Granpa died but she will always be hearing about him.

A little about Allan

Whilst Allan’s working life began as a draughtsman in the shipyards, at 23 he went into food sales where he worked his way up to sales director. In 1999, together with his business partner, Graham, they set up their own food marketing company, “RSS”, employing 100 people.

Allan loved watching St Mirren Football team, but his two main hobbies were golf and bowls which he was very good at. I shared his love of bowls, and two months before he died we entered and won a mixed pairs competition, receiving a cup engraved with our names, and with which I am delighted. He was such a good sport.

Diagnosed with Paget’s Disease

Allan had a sore leg when he went for a medical in 2007. Blood tests showed that his Alkaline Phosphatase (ALP) level was quite high. From this, Paget’s disease in his pelvis, was diagnosed. Little did we know then that he would die from a very rare complication of the condition just 7 years later.

He was initially prescribed treatment, which was a 2 month course of Risedronate tablets. Each time he received the treatment, which was about every eighteen months, his ALP levels went down. Throughout that time he was never in pain and life continued as normal.

Something Changed

It was in January 2013 that something changed. Allan’s leg, below his knee, became painful. He said it felt like it was in a vice. He had the Paget’s treatment again but this time the tablets didn’t work. He went back to the consultant quite a few times and had many scans which threw up nothing abnormal. By this time he was walking with a noticeable limp.
We went on a cruise through the Panama Canal in April 2013 and, although Allan never complained, he was in absolute agony. When we came home he contacted his consultant who carried out blood tests. His ALP level was over 2000. We were extremely worried, although all his other tests were clear. Allan was taking all kinds of painkillers but nothing was working. The consultant suggested giving him different Paget’s medication via a drip (Zoledronic Acid). Despite this he was still in agony. It was the end of May and we were distraught because this wasn’t normal.

Allan was sent for scans and a radiologist spotted an abnormality which he didn’t think was Paget’s disease. On 4th June we were told that he had a cancerous tumour in his pelvic bone. I knew this was coming. Allan didn’t. He was always so positive.

Allan had developed Paget’s-associated osteosarcoma, a rare bone cancer that occurs in less than 1:1,000 of patients with Paget’s disease. He was in a private health scheme, however, because of the cancer he was transferred back to the NHS. It was over two months before he could start chemotherapy treatment. Each day seemed like an eternity. Life was torture. Allan continued to golf and bowl. He would never give up.

On August 16th 2013, he started a 3 weekly cycle of chemotherapy. Around that time a lump appeared on his skull. This was bone cancer as well but was successfully removed in March 2014. He had 6 ½ weeks of radiotherapy with an operation before and after to insert a “spacer” device into his pelvic area which would aid the treatment. By this time it was June. He still golfed and bowled. Alan was positive that the treatment would be successful. He said it was a blip.

On the 22nd of June 2014 he played golf at the Turnberry resort on the Ayrshire coast. He looked so well. Apart from a limp you would never know. The following day he coughed up a spot of blood. The cancer had spread to his lungs. This was the start of a rapid decline. Within three weeks he couldn’t breathe without oxygen, was in a wheelchair and he died at home on 1st August 2014.

Everybody loved Allan. He made a wonderful life for his family by creating a successful business and being a super husband, father and grandfather. The first we knew his condition was terminal had been the 10th of July last year. How I wish we’d never been told. The last few weeks were horrendous. Allan was so brave, so positive. He never gave up. He always made me laugh.

The medical team who were dealing with Allan’s cancer appeared to know very little about Paget’s disease. I wish more professionals and people generally were more aware of it. It took such a long time to diagnose his cancer because it is so rare for someone with Paget’s disease to develop associated cancer.
We have all been deeply affected by this and it has certainly raised awareness of Paget’s disease and Paget’s-associated osteosarcoma. Allan’s business was UK wide and he took part in many events, he touched many people’s lives and many are now aware of the devastating illness that took him from us.

I didn’t contact the Paget’s Association until March 2014 because I hadn’t known they existed. It was only when we started to panic that we looked on the internet to see if we could get advice and found the Association’s website.

Raising funds to support research

There has got to be more research into Paget’s disease and Paget’s-associated osteosarcoma. With this in mind we set about fundraising and on what would have been our 35th Wedding Anniversary, in October, fifteen of us cycled around Millport on the Isle of Cumbrae which is over 10 miles. Our little granddaughter, Sophie, came too. Allan only got to know her for a short while but she was his pride and joy.

Allan’s best friend, Norman Kerr, set up a Just Giving Page which has so far raised over £4,100. So many people have donated including all of Allan’s work colleagues. Norman worked for Allan too and he is planning a sponsored cycle across Scotland, on Allan’s birthday.

Here are some of the events that have taken place to raise funds for the Paget’s Association in memory of Allan:

- The son of my best friend Toty plays in a band called Vasa and they had a door collection which raised £150.
- Toty’s daughter, Lynsey, was sponsored to run 10K.
- A coffee morning was held in a special needs school.
- My daughter’s friends did a Muddy Assault Course.

This year, our bowling club, Mearns Bowling Club are having a competition. I am providing a cup in memory of Allan and Paget’s. We will make it a yearly event.

When Allan was diagnosed with Paget’s disease we just didn’t realise the seriousness of it. We never thought for a moment that it could turn into cancer. I know it’s rare and don’t want to worry people that this could happen but it was very distressing for us all to see Allan in so much pain, and despite tests nothing was found initially because it is so hard to detect. If anyone finds themselves in a similar situation and would like to talk about it I am more than willing to help. Please just contact me through The Paget’s Association. We’d love the money raised to be used for research.

Norma

Supporting Research in Memory of Allan

The Paget’s Association want to ensure that the funds raised are used to support research into the condition. We are pleased to announce that Alan’s family and friends have agreed that the money collected in memory of Allan, should be used for a bursary in Allan Reid’s name, to help to support a young researcher working on Paget’s disease. It will be a fitting and lasting memory of Allan.