RATIONAL TESTING

Investigating an incidental finding of a paraprotein

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

Previous articles in this series

- Investigating asthma symptoms in primary care (*BMJ* 2012;344:e2734)
- Diagnosis of Helicobacter pylori infection (*BMJ* 2012;344:e828)
- Raised inflammatory markers (*BMJ* 2012;344:e454)
- Investigating recurrent angio-oedema (*BMJ* 2011;343:d6607)

A paraprotein can have many causes—some serious but others unlikely ever to cause any problems. This article outlines key investigations and some of the difficulties that may arise after the incidental finding of a paraprotein

A 61 year old man with no significant medical history is found to have an elevated total protein and globulin level after routine private health screening in relation to his employment. He is referred to his general practitioner for evaluation. He reports being "completely well" other than occasional back pain and takes no regular medications. Further investigation with serum protein electrophoresis reveals that he has a paraprotein at a concentration of 21 g/L (any measured paraprotein is an abnormal finding)

What is the next investigation?

Raised serum globulin or total protein, or both, is often the first indication of the presence of a paraprotein. The level of globulin in the serum is derived by subtracting the albumin concentration from the total protein. All globulins are produced by plasma cells in the bone marrow. When a raised globulin level is found, it is important to determine the cause of the increased production of immunoglobulin:

- *Polyclonally increased plasma cells*—a reaction to several different disease processes including inflammation, infection, liver disease, and cancer

– or

- *Monoclonal proliferation of plasma cells*—resulting in a monoclonal immunoglobulin or paraprotein.

Serum protein electrophoresis or immunofixation

Serum protein electrophoresis and immunofixation are used to distinguish between polyclonal and monoclonal immunoglobulins (see figs 1 and 2). With the former, which is more common, the raised globulin may be accompanied by raised inflammatory markers and anaemia and should not trigger routine haematology referral. In the present case, however, the patient has been found to have a paraprotein on serum protein electrophoresis.

LEARNING POINTS

Raised serum globulin concentration or total protein may be the first indication of a paraprotein, but a raised globulin level is more commonly due to polyclonally raised globulins in reaction to inflammation, infection, or cancer

A paraprotein is detected by serum protein electrophoresis and then further characterised by immunofixation

Evaluate any patient with a newly detected paraprotein for symptoms or signs of myeloma or other lymphoproliferative disorder, both clinically and with investigations

Most patients with a newly detected paraprotein will have monoclonal gammopathy of undetermined significance (MGUS) and will never progress to a condition that requires treatment

A paraprotein is not uncommonly identified during investigation of unrelated symptoms or after routine health screening, and most will be classified as monoclonal gammopathy of undetermined significance (MGUS). Identification of a paraprotein presents clinicians with the challenge of deciding whether and how far to investigate. MGUS can be detected in the serum of about 3% of people aged over 50, and most studies indicate that the incidence increases with age.[1]

MGUS is defined as the presence of a monoclonal protein (paraprotein) in the serum or urine of an individual with no evidence of myeloma, amyloid light chain amyloidosis, Waldenström's macroglobulinaemia, or related disorder (see table) and no myeloma related organ or tissue impairment (box 1).[2] All listed criteria need to be met to make a diagnosis of MGUS.

The distinction between symptomatic myeloma and MGUS or asymptomatic myeloma depends on the presence or absence of myeloma related organ or tissue impairment, and the relevant criteria are shown in box 1. Patients with asymptomatic myeloma do not require immediate treatment but do have a higher risk of progression and should be followed by a haematologist.

On average the cumulative risk to an individual of transformation of MGUS to myeloma or other lymphoproliferative disorder is 1% a year, and the risk continues even after 25 years.[3] Patients with myeloma or other lymphoproliferative disorder and those patients with MGUS with the highest risk of progression need to be identified and referred promptly to a haematologist. Conversely, it is important to identify patients with low risk MGUS so as to avoid over-investigating patients with a low risk of current or future serious disease.

Clinical evaluation

Patients with MGUS, by definition, do not have symptoms relating to their underlying diagnosis. However, it is important when a paraprotein is detected that the patient is formally evaluated for symptoms, signs, and abnormal test results suggestive of myeloma, lymphoma, or amyloid light chain amyloidosis (see box 2). If detected, further appropriate confirmatory laboratory investigations are required in addition to tests described below.

Further investigation

When a new paraprotein is detected, it would be considered normal practice for a laboratory to automatically carry out the following tests to further define the size and type of the paraprotein:

- *Paraprotein quantification*—Usually by densitometric measurement of the paraprotein band on serum protein electrophoresis (see fig 1)
  - A low concentration of paraprotein makes MGUS more likely, whereas a high concentration is more commonly associated with myeloma or Waldenström's macroglobulinaemia
  - However, amyloid light chain amyloidosis is often associated with a low level paraprotein, and myeloma

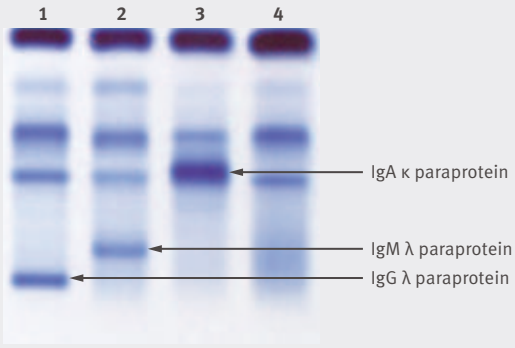

Fig 1 | Serum protein electrophoresis showing examples of patients with a paraprotein and normal polyclonal immunoglobulins

Lane 1 shows an IgG λ paraprotein of 7 g/L
Lane 2 shows an IgM λ paraprotein of 8 g/L
Lane 3 shows an IgA κ paraprotein of 28 g/L
Lane 4 shows normal polyclonal immunoglobulins

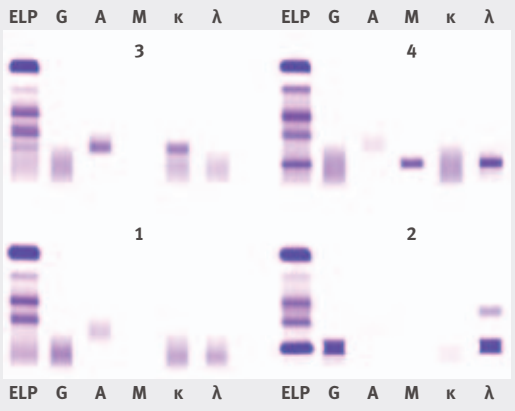

Fig 2 | Four serum samples processed for immunofixation. In each panel the same serum has migrated along six tracks that have then been stained for protein (ELP); for IgG, IgA, or IgM heavy chains; or κ or λ light chains

Panel 1 is normal serum with polyclonal immunoglobulins
Panel 2 is serum with high level of IgG λ monoclonal immunoglobulin with monoclonal λ free light chains and little polyclonal immunoglobulin; the patient had myeloma with renal failure
Panel 3 is serum with low concentration IgA κ paraprotein
Panel 4 is serum with IgM λ paraprotein

Box 1 | Myeloma related organ or tissue impairment*

- Calcium concentration increased—Corrected serum calcium >0.25 mmol/L above the upper limit of normal or >2.75 mmol/L
- Renal insufficiency attributable to myeloma
- Anaemia—Haemoglobin 20 g/L below the lower limit of normal or <100 g/L
- Bone lesions—Lytic lesions or osteoporosis with compression fractures (magnetic resonance imaging or computed tomography may clarify)
- Other—Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months)

*Adapted from International Myeloma Working Group[2]

can also occur with a low paraprotein level
  - The level of the paraprotein is also important in determining the risk of future progression once MGUS is confirmed (see below)
- *Definition of the immunoglobulin class* of the paraprotein by immunofixation (immunoglobulin heavy and light chain isotype)
  - This is important as the type may direct future investigations. Myeloma is commonly associated with an IgG or IgA paraprotein, rarely IgD or IgE (see fig 2). IgM paraproteins are more commonly associated with lymphoproliferative disorders such as Waldenström's macroglobulinaemia or low grade lymphoma
- In addition, the following laboratory and radiological tests should be carried out in all patients with a new paraprotein to exclude conditions in box 2 and (once these are excluded) to evaluate MGUS:
  - *Serum immunoglobulin levels* to determine presence or absence of immune paresis (a reduction of residual normal immunoglobulin levels). This is important as low immunoglobulin levels in conjunction with recurrent bacterial infection are considered a "minor" criterion for the diagnosis of myeloma if other criteria are met
  - *Urinary protein estimation and urinary protein electrophoresis* on a random urine sample to rule out a high urinary protein level suggestive of Bence Jones myeloma or nephrotic syndrome
  - *Full blood count*
  - *Serum creatinine, urea, and electrolytes*
  - *Serum calcium*
  - *X rays of areas of skeletal pain*.

The outcome

The patient is found to have an IgG κ paraprotein at a level of 21 g/L with normal serum immunoglobulin levels. There is a longstanding history of intermittent low back pain, physical examination was unremarkable, and investigations did not reveal anaemia, renal impairment, or hypercalcaemia (which might point to a diagnosis of myeloma). The urine was positive for Bence Jones protein at a low level. X ray of the lumbar spine shows mild degenerative changes only. The patient remains anxious.

Should this patient be referred?

MGUS is common, and primary care and other physicians often have difficulty in knowing which patients to refer to a

Diagnostic criteria for monoclonal gammopathy of undetermined significance (MGUS), asymptomatic myeloma, and symptomatic myeloma*

MGUS	Asymptomatic myeloma	Symptomatic myeloma†
Paraprotein in serum <30 g/L	Paraprotein in serum >30 g/L *or*	Paraprotein in serum or urine‡
Bone marrow clonal plasma cells <10%, low level of plasma cell infiltration in a trephine biopsy (if done)	Bone marrow clonal plasma cells >10%	Bone marrow (clonal) plasma cells
No myeloma related organ or tissue impairment (including bone lesions or symptoms)	No myeloma related organ or tissue impairment (including bone lesions or symptoms)	Myeloma related organ or tissue impairment (including bone lesions or symptoms)
No evidence of other B cell lymphoproliferative disorder or amyloid light chain amyloidosis or other light chain, heavy chain, or immunoglobulin associated tissue damage§		

*Adapted from International Myeloma Working Group.[2]
†Patients without symptoms but with significant myeloma related organ damage are grouped with symptomatic myeloma because of the need for treatment.
‡No specific level required for diagnosis. A small percentage of patients have no detectable paraprotein in serum or urine but do have myeloma related organ or tissue impairment and increased bone marrow plasma cells (non-secretory myeloma).
§Amyloid light chain amyloidosis and the neurological syndromes related to IgM paraprotein are examples of monoclonal gammopathy associated with specific syndromes.

Box 2 | Symptoms, signs, and abnormal test results associated with myeloma, lymphoma, and amyloid light chain amyloidosis

Myeloma
- Bone pain
- Hypercalcaemia
- Renal failure
- Anaemia
- Hyperviscosity

Lymphoma and other lymphoproliferative disease
- Symptoms (such as night sweats, fever, weight loss)
- Lymphadenopathy
- Hepatosplenomegaly
- Hyperviscosity (especially if IgM paraprotein) resulting in, for example, headache, retinal vein engorgement
- Pancytopenia

Amyloid light chain amyloidosis
- Carpal tunnel syndrome
- Peripheral neuropathy
- Macroglossia
- Unexplained heart failure
- Nephrotic syndrome

Box 3 | Which patients with a paraprotein should be referred for specialist review?
- Symptoms or signs of myeloma or lymphoproliferative disorder
- Unexplained blood test or x ray results (such as raised creatinine or calcium concentrations)
- IgG paraprotein >15 g/L
- IgA or IgM paraprotein >10 g/L
- IgD or IgE paraprotein at any level (rare)

consultant haematologist. The cumulative risk of progression (to multiple myeloma from IgG and IgA MGUS and to other malignant lymphoproliferative disorders from IgM MGUS) is about 1% a year. However, because of the high median patient age at the time of detection of a paraprotein and the existence of diseases not associated with the paraprotein, the risk that a patient with MGUS will develop myeloma or related disorders in his or her lifetime is considerably lower.[3] Not all patients with MGUS need to be referred to a haematologist.

Criteria for referral and further investigation are set out in box 3. These referral criteria are based on strong associations with risk of progression.

- High level of paraprotein (>15 g/L if IgG or >10 g/L if IgA or IgM)[3]
- Paraprotein not of IgG class[3]
- Level of bone marrow plasma cell infiltration[4]
  - Evaluation of bone marrow plasma cell infiltration requires referral to a haematologist
- Abnormal serum free light chain ratio[5]
  - This relatively new serum assay for free light chain[6] detects levels of both κ and λ immunoglobulin light chains. A recent study has shown that patients with MGUS who have abnormal levels of or an abnormal κ to λ ratio of light chains in the blood are more likely to progress to active myeloma.[5] However, serum light chain levels are also raised in patients with renal impairment. This test should not be carried out in primary care or by general physicians except under the direction of a haematologist experienced in its interpretation. If advised, a request for serum free light chain assay should be made.

Importantly, variables such as the presence of Bence Jones proteinuria, immunosuppression, age, and sex have not been found to have predictive value for progression.[7]

Based on data from a number of studies, a simple risk stratification model for progression has been proposed for use by haematologists that entails measurement of the size and type of paraprotein and of the serum free light chain ratio.[5]

The patient is referred in view of his relatively high paraprotein, chronic back pain, and anxiety. Further investigations show that he has a normal serum free light chain ratio, bone marrow plasma cell infiltration <5%, and normal skeletal survey, confirming that he does not have myeloma.

What happens next?

There are no definite rules regarding follow-up of MGUS, but guidance is based on the estimated risk of progression.[8 9]

This patient is reassured that there is no evidence of myeloma or other lymphoproliferative disorder. He is advised that, although MGUS can progress to a malignant condition, the overall risk of progression is relatively low at around 20% over 20 years.[3] The condition does not require active treatment, but rather a "watch and wait" approach. His own risk of progression based on the risk stratification model is "low intermediate," so lower than the "average" for all patients with MGUS, providing some further reassurance.

The patient is referred for follow-up to an outreach service designed to use local phlebotomy services with central haematologist review of laboratory parameters and symptoms identified by a self assessment questionnaire. (This is an increasingly popular follow-up model in the UK designed to reduce the burden of follow-up on primary care physicians and avoid unnecessary haematology clinic visits while allowing some specialist input.[10]) He and his general practitioner are given information sheets that include details of symptoms that might trigger a re-referral (such as fatigue, recurrent infections, unexplained bleeding, bone pain, weight loss). It is recommended that blood tests for paraprotein level, full blood count, serum creatinine, urea, electrolytes, and corrected serum calcium be carried out every three months initially, with the interval extending to six or 12 months if results remain stable and no symptoms are reported.

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Patient consent not required (patient anonymised, dead, or hypothetical).

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A PATIENT'S JOURNEY

Ulcerative colitis

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

Previous articles in this series

- At either end of the tube (*BMJ* 2012;344:e2971)
- Superficial spreading melanoma (*BMJ* 2012;344:e2319)
- Polymyositis (*BMJ* 2012;344:e1181)
- Mood disorder in the perinatal period (*BMJ* 2012;344:e1209)

A student in her 20s recounts her complicated journey to a diagnosis of ulcerative colitis. As her symptoms progressively worsened, she overcame her embarrassment and sought further help in reaching a diagnosis

I remember being mortified at the thought of seeing a doctor about a prolapsed haemorrhoid at the age of 23. My journey had started in the summer of 2007, in central Asia, while I was on a university work experience programme. For over a month I suffered from constant diarrhoea. Everyone around me explained that this was a normal part of travelling and that I should try and see the funny side. However, I found the symptoms intolerable. On my return to the UK a month later, my general practitioner sent a sample for microbiology, which came back positive. I was prescribed a single dose of antibiotic and the diarrhoea improved.

However, over the following year (my final year of undergraduate studies) I was never quite right. But I took too long to go back to a doctor about my bowel problems. By the time I went to my GP in February 2009, during my MSc course, I had been passing blood and mucus for about three months. My delay in seeking further medical help was caused by the gradual and intermittent onset of the symptoms and, of course, by my own embarrassment.

When I went to see my new GP she sent me for blood tests, which showed raised inflammatory markers, and referred me for a flexible sigmoidoscopy. I had gradually become more and more exhausted and everyday activities were requiring increasing amounts of stamina. During my first degree I had been a keen member of the hill walking club and had walked 10 Munros in a weekend; now a walk to the supermarket was a struggle. I went back to see my GP and explained that I was finding things very difficult, my abdomen was distended, and my friends had told me I had turned grey. However, she said I should wait for the flexible sigmoidoscopy at the hospital.

A couple of weeks after seeing my GP, while I was at home in the house I shared with student friends, it felt as if my bowel had prolapsed. I was then in the very unusual situation of having to explain this to my new boyfriend. He insisted on having a look and, not being a doctor, decided it looked like a large prolapsed haemorrhoid. On seeing my toilet bowl filled with blood and mucus, however, he took me to the Saturday drop-in medical centre. I remember being mortified at the thought of seeing a doctor about a haemorrhoid and I put a full face of make-up on in an effort to make myself as attractive as possible.

In the accident and emergency department attached to the drop-in centre, the doctor took my history—I explained the raised inflammatory markers and the suspected inflammatory bowel disease. He did a rectal examination, which was incredibly painful, misdiagnosed an anal fissure, prescribed Anoheal (diltiazem hydrochloride 2% cream), told me to chase up my flexible sigmoidoscopy, and discharged me.

At this point I felt incredibly helpless and could feel myself fading away. My boyfriend put me on a train to my parents and I stayed there for the rest of the weekend. I spent Sunday on the sofa and tried lying on my front on the floor to stop myself from going to the toilet because it was so unbearable. On the Sunday night I remember passing a continuous stream of blood for four seconds. I could hardly move after this and struggled back to bed. In the morning my mother came in to see me; she later told me that for the first time she had realised what the critical care nurses meant when they said a patient was "going off."

My mother took me to the accident and emergency department and I was sent in to see a doctor immediately. The doctor ordered a full body x ray, admitted me to acute medical care, and put me in the hands of the gastroenterologists. By this time I was so weak that I could hardly lift my arm and needed all of the electric features on the hospital bed. That afternoon I was diagnosed by a consultant gastroenterologist as having ulcerative colitis and was prescribed intravenous steroids. I was finally in safe hands, where I needed to be, and getting treatment.

Difficult hurdles

Ironically, receiving the diagnosis of ulcerative colitis was not one of the difficult points that stand out in my memory. I was so happy to be in hospital that the diagnosis paled in comparison. After three days in hospital my condition had completely stabilised, in rather a miraculous fashion. However, after I had left hospital and as my steroid dose was tapered down, the ulcerative colitis relapsed and I had to go back into hospital for six days of intravenous steroids. This was certainly a low point as I came to understand the chronic nature of my illness.

Being prescribed azathioprine and reading the patient information leaflet one night in the hospital was another low point. The leaflet stated that a common side effect from azathioprine was cancer. It suddenly sunk in how serious

LATE DIAGNOSIS

My journey to diagnosis was not a smooth one, and I have spent many months wondering how and why I almost bled to death in a student house. Some of the factors that I believe contributed to my late diagnosis are listed below.

- My symptoms did not quite fit the textbook
- The pain I experienced outside the bathroom was an intermittent, dull ache and I remember describing it to my GP as not being as bad as period pains
- As a hill walker, I had learnt to keep going and push myself and maybe this attitude did not help me to help myself
- Ulcerative colitis has a very low media profile so I was not able to self diagnose and I thought it was irritable bowel syndrome
- Some of the doctors I saw did not realise how severe ulcerative colitis could be and had experience of dealing only with mild forms of the condition
- At the time of onset of symptoms I did not have an established relationship with a GP, and between onset and stabilisation of the colitis I lived in four different cities, so having to overcome embarrassment to see new doctors all the time was difficult
- The toilet in one of my student flats had a dark bowl and was poorly lit
- I hid my grey face and embarrassment with make-up when I went to the accident and emergency department for the first time

A DOCTOR'S PERSPECTIVE

Ulcerative colitis is an inflammatory disorder of the colon, leading to bloody diarrhoea. It has a prevalence of about 200 per 100 000 population and often presents at age 15-30 years. The inflammation begins in the rectum and is continuous, extending along the colon for a variable distance. The cause is unknown, but a disordered immune response to a luminal agent, probably commensal bacteria, is the likely mechanism. Smoking is protective, and it is not uncommon for symptoms to begin soon after stopping smoking. Ulcerative colitis often has a remitting and relapsing pattern of disease activity, though continuous symptoms of varying severity are also common.

Diagnosis is usually straightforward, with typical appearances being evident at initial mucosal inspection, often by sigmoidoscopy. However, such patients have to reach a gastroenterologist first, which is not as easy as we might think.

Patients are often embarrassed to talk about their bowels and may put up with symptoms rather than seek help. Delays can also occur when blood loss is less of a feature or is erroneously believed to have its origins in the anal canal. Such patients can be labelled as having irritable bowel syndrome for a considerable length of time. This may then be compounded by incomplete or inaccurate assessment at the initial contact with medical professionals, which seems to have happened with this young woman.

I believe that as gastroenterologists we are mindful of how inflammatory bowel disease can affect our patient's lives. They often present at a time when they want to be getting on with their lives and careers, only to be knocked back by the morbidity that can come with colitis, the need to take regular medication, and the label of having a "chronic" condition. At times I think we can underestimate the impact such an illness can have, perhaps particularly as it is something we see all the time. This young woman's journey demonstrates a huge impact on her life.

At diagnosis an explanation of the condition, treatments, and expected progress are important. Our inflammatory bowel disease nurses are helpful at this point and have more time than doctors to discuss this and explore patients' perceptions and concerns.

Many patients do well with oral and topical mesalazines. Those who need more than one course of steroids are offered immunosuppression with thiopurines. These agents are usually well tolerated but can cause problems. When we suspect that patients may need to step up their treatment we discuss these drugs with them and give them lots of information, in the form of leaflets and website resources. This case is a reminder of the shortcomings of the patient information leaflets in medication boxes. They can be at best unhelpful, woefully out of date, and not relevant to many of our patients.

Ulcerative colitis is a chronic condition and most patients need to take treatment daily. This can act as a negative daily reminder that they have such a chronic condition, and at times it may be difficult for them to see any light at the end of the tunnel. Our specialist nurses play a pivotal role here, being a prompt point of contact for patients with such concerns, for advice about relapses, not responding to initial stepping up of treatment, or indeed any other problems. Patients really appreciate help being readily at hand, by phone or email, and value the extra time our nurses can give them.

Biological treatments such as infliximab and adalimumab have transformed our management of Crohn's disease, but their exact role in ulcerative colitis is unclear. They are likely to be useful, but better studies are needed to confirm this, as recent studies of these agents in ulcerative colitis are flawed and have resulted in funding agencies restricting access. This area needs urgent attention, particularly as the only alternative may well be a colectomy.

Sean Kelly, *consultant gastroenterologist*

the condition was if I had no choice but to take this cytotoxic medication every day for the foreseeable future. However, six weeks later I began projectile vomiting, so the azathioprine was swapped for mercaptopurine.

The next difficult step was when I started to lose blood again, in September 2009, despite being on mercaptopurine and a low dose of steroids. I spent the week before a flexible sigmoidoscopy in a terrified state, fearing that I would need a colectomy. However, the sigmoidoscopy showed only mild localised inflammation.

One of the most difficult things of all was taking steroids for eight months: in the end I was desperate to come off them. I had put on a huge amount of weight and my face had changed so much that even close relatives did not recognise me.

The immunosuppressive cocktail of medication that I was taking added another equally difficult hurdle: the proliferation of tiny plantar warts on my face. I first went to my GP when I had one wart, but this was not recognised and by the time I went back I had over 10 warts on my face. This was the final straw. I had gone from being a sporty young woman to one with a huge round face with warts on it. Cream treatment and cryotherapy provided some benefit but did not remove the one original and very stubborn wart. Laser treatment was not approved for me and the only remaining option was cautery and curettage. Appalled at the thought of someone taking a scalpel to my face I went to a private clinic and had my warts removed by radiosurgery, a novel and unusual treatment I am told, but one that worked excellently and has left me without scars.

Looking forward

It is now three years since I was diagnosed. The mecaptopurine, mesalazine, and occasionally a rectal prednisolone foam have more or less kept the ulcerative colitis under control, although it is worse when I catch a cold, which happens more often as I am immunosuppressed.

It has been an adjustment learning to live with a chronic illness, learning not to push myself (contrary to all that training in the Scottish highlands), and taking rest when it is needed. The condition is debilitating, and in some respects the term "disability" fits it better than "illness," although describing myself as disabled is something that I still have not come to terms with. The inflammatory bowel disease specialist nurses provide an excellent service, and expert help is only a phone call or an email away.

I am now in my third year of a PhD in a laboratory researching the production of recombinant proteins in mammalian cells. Although my symptoms are managed so that I can live my life, flare-ups still occur from time to time, which are short lived and do not require admission to hospital but do necessitate time out of the laboratory. If my ulcerative colitis did relapse significantly I would like to think that monoclonal antibodies would be offered to me before a colectomy.

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