

# Metal-induced generalized pruriginous dermatitis and endovascular surgery

ANA GIMÉNEZ-ARNAU, VICENTE RIAMBAU<sup>1</sup>, ESTHER SERRA-BALDRICH AND JOSÉ G. CAMARASA

Department of Dermatology, Hospital del Mar; <sup>1</sup>Institut de Malalties Cardiovasculars, Hospital Clinic, Barcelona

Metal contact allergy is a common problem in the general population. Diagnostic and therapeutic medical-surgical procedures in which metals can be responsible for eczema are diverse. Endovascular aortic surgery is still an experimental but less invasive technique. A generalized eczematous dermatitis elicited by metal of an endovascular prosthesis is presented. An abdominal aortic aneurysm was diagnosed in a 79-year-old woman. Endoluminal repair with a straight Vanguard<sup>®</sup> endograft was successful. 3 weeks later, she suffered a severe episode of erythema and eczema on the legs. Since then, she complained of continuous pruritus with eczema and excoriated papules. The dermatitis and also the patch test pathology showed eczema. Patch testing was positive to nickel sulfate and cobalt chloride. An endograft semi-quantitative metal analysis was performed with plasma-induction joint mass-spectrometry. The self-expanding metal stent was mainly composed of nickel (~55%) and titanium (21%) with reinforcing thread of platinum. Antimony was detected only in the polyester textile. These results are consistent with Nitinol<sup>®</sup> composition. The need for preoperative patch testing for metals is controversial. Enquiry about metal allergy is recommended before endoluminal surgical procedures. In the near future, the design of endografts must take into account the possibility of this sort of reaction.

**Key words:** dermatitis; eczema; nickel sulfate; endoprosthesis; endograft; abdominal aortic aneurysm; systemic contact dermatitis. © Munksgaard, 2000.

*Accepted for publication 6 March 2000*

An arterial aneurysm is a localized permanent dilatation of an artery. The amount of dilatation required for an artery to be classified as aneurysmatic is controversial. The diameter of an aneurysm must be at least 50% greater than the anatomical diameter of reference. The spontaneous rupture of an abdominal aortic aneurysm (AAA) is potentially fatal. The natural evolution of an aneurysm is its rupture, unless the patient dies from another cause first. Rupture can occur in aneurysms of any size, with greater risk associated with the larger ones. Aneurysm rupture mortality is estimated to be more than 80%. Of all ruptured AAAs, only a minority of patients reach hospital alive and can be operated on. Hospital mortality for ruptured AAA operations oscillates between 40–50%. Ruptures usually occur in patients who have ignored the existence of their aneurysm. For these reasons, prophylactic interventions are recommended for AAAs in asymptomatic patients with aneurysms  $\geq 5$  cm in diameter. Hospital mortality rate for surgical repair of non-ruptured aneurysms is 7% and morbidity 21% (1). In these cases, a direct aortic

approach is performed by laparotomy. The trauma deriving from the laparotomy and the haemodynamic aftermath due to prolonged pinching of the aorta are the main causes of the postoperative complications.

In an attempt to reduce the risk of prophylactic surgery of AAAs, a minimally aggressive surgical technique has recently been developed. Endovascular management of aneurysms is based on indirect access to the aneurysm by an endovascular route through the femoral or iliac arteries. Dissection of the common femoral artery is sufficient to be able to insert an endograft into the aneurysm.

The endovascular prosthesis is composed of a synthetic fibre and a metallic anchoring system or stent. The first clinical results of AAA endovascular grafts or implants were published by Parodi et al. (2) and by Volodos et al. (3) in 1991. In 1993, the FDA approved the first Endo Vascular Grafting System<sup>TM</sup> for clinical testing. This included endoluminal surgical equipment consisting of the endovascular prosthesis and the introducer system. The system was designed for elective treatment of

Table 1. Diagnostic and therapeutic medical-surgical procedures in which metals can be involved in causing contact dermatitis

|                                             | Reference                |
|---------------------------------------------|--------------------------|
| Orthopaedic surgery                         | Gawkrödger et al. (1993) |
| Use of intrauterine device                  | Barranco (1972)          |
| Amputation prosthetisation                  | Manneschi et al. (1989)  |
| Electrocardiograph                          | Rietschel et al. (1995)  |
| Pacemakers                                  | Brun et al. (1980)       |
| Transcutaneous nerve stimulation electrodes | Rietschel et al. (1995)  |
| Acupuncture                                 | Romaguera et al. (1979)  |
| Ocular prostheses, glasses                  | Jirasek et al. (1976)    |
| Stethoscope                                 | Rietschel et al. (1995)  |
| Dental prostheses                           | Vilaplana et al. (1994)  |
| Endovascular surgery                        |                          |

certain very well selected and asymptomatic infra-renal AAAs.

The surgical procedure requires a well-coordinated team of surgeon, radiologist and anaesthetist, since success depends on good indication, good selection and design of the prosthesis and adequate visualization of the problem and the procedure, together with eventual surgical support in case of any complications.

This technique is still in the clinical experimentation stage and its long-term efficacy and safety need to be assessed. This is why the approved teams need adequate training, and application must follow the canons currently in effect in international registers.

Cutaneous allergy induced by contact with metals is a frequent phenomenon in the general population. Diagnostic and therapeutic medical-surgical procedures in which metals can be responsible for eczema are diverse (Table 1). Eczema or allergic dermatitis caused by orthopaedic implants, e.g., is an infrequent complication, controversial, difficult to diagnose and still under discussion. Nevertheless, the potential for sensitization to implanted metal alloys has been assessed in various clinical studies. Nickel can be released, e.g., from stainless steel prostheses used in orthopaedic surgery by sweat, blood and physiological saline solutions (4, 5).

The objective of this study is to present the 1st clinical case of disseminated eczema provoked by the metal contained in an endovascular implant. Thus, endovascular surgery could be included as a new diagnostic and therapeutic medical-surgical procedure capable of inducing dermatitis and/or eczema.

### Patient, Material, Methods and Results

#### Clinical case

A 79-year-old woman was diagnosed by echography to have a 6-cm diameter abdominal aortic saccular aneurysm of arteriosclerotic origin sus-

ceptible to elective treatment. The patient's age and co-morbidity made her a candidate for elective endoluminal surgery. She was affected by essential arterial hypertension, hypercholesterolemia and chronic obstructive pulmonary emphysema. Endovascular surgery was performed and a straight Boston Scientific Vanguard® endoprosthesis was placed in July 1998. The procedure was successful as axial computerized tomography confirmed exclusion of the aneurysm, and angiography confirmed normalization of blood flow.

3 weeks later, a cutaneous eruption appeared. It consisted of severe pruritus accompanied by eczematous erythema on the lower limbs. This resolved with oral antihistamines and topical corticosteroids. Since then, she had complained of pruritus and the presence of disseminated eczematous lesions was observed, mainly on the abdomen but also on the lower limbs and occasionally on the back and arms. She came to our centre during one of these episodes. In a detailed anamnesis of her cutaneous symptoms, the patient spoke of intolerance of jewellery metals and mouth-burning pain after using a metallic dental prosthesis.

A clinical and diagnostic study of the patient was initiated. It included a biopsy of her eczema, patch tests with standard and special series of metals and biopsy of the positive reactions.

Suspecting that the clinical picture could be caused by the release of metal into the blood through the endoprosthesis placed endoluminally in the abdominal aorta, liberation of nickel by the endoprosthesis was studied with the dimethylglyoxime test and the metal composition of the stent with plasma-induction joint mass-spectrometry (ICO-MS).

#### Complementary tests

Biopsy of the cutaneous lesions showed the typical histology of eczema, with the presence of spongiosis, intracellular oedema and intra-epidermal vesicles. Moderate acanthosis and parakeratosis

were observed. The papillary dermis presented vascular dilatation, oedema and a mononuclear cellular infiltrate situated around the superficial capillaries permeating the epidermis.

The patch tests performed with the standard and the special series of metals were positive after 4 days to nickel sulphate (++) and cobalt chloride (+++). Patch tests with titanium (1% pet.) and platinum (tetrachloroplatinate 0.25% aq.) were negative. The histology of both the sample taken from the positive patch to nickel sulfate and for cobalt chloride after 4 days showed a dermal lymphohistiocytomatous inflammatory infiltrate, with a tendency to spongiosis and exocytosis, typical of incipient acute contact eczema.

### Endoprosthesis study

A study was made of an endoprosthesis of the same brand and model as the one implanted by way of sample for successive analyses.

To show the release of nickel in metallic objects, the dimethylglyoxime test was used. This test is performed with a few drops of dimethylglyoxime in an alcoholic solution of 1%, to which a few drops of ammoniac water has been added. This solution is put in contact with the metallic object to be investigated. The dimethylglyoxime test was negative with the endoprosthesis.

A semi-quantitative determination of metal was performed with the plasma induction joint mass spectrometry technique on a Perkin Elmer ELAN 6000 apparatus under standard conditions.

The stent had 3 different parts and each was analysed separately. There was a grey metallic mesh, a blue reinforcement consisting of a polypropylene thread, and some metallic parts that formed spiral joints to reinforce the mesh.

The polypropylene thread sample (6.9 mg total) was digested with nitric and perchloric acid (Baker Instra) in a closed Teflon reactor in a Milestone microwave oven. The metallic mesh (70.6 mg) and the metallic reinforcement (31.3 mg) samples were digested with aqua regia and hydrofluoric acid (Baker Instra) in a closed Teflon reactor in a Milestone microwave oven. The dissolved samples were increased to 13 g with Milli-Q grade deionized water by weight. 4 blanks were placed in parallel with the samples. The results were expressed in mg/Kg (ppm). It is admitted that the semi-quantitative analysis has a margin of error of 10–15% for minority elements and for trace quantities. The error for majority elements can be even greater. This is why only an indication of which were present and an approximate % was offered.

The majority component in the metallic mesh was Ni (~55%) and in the metallic reinforcement,

Pt (~60%). The quantity of Ti in the mesh was ~21% while the quantity of Co was 2 ppm. The metallic components detected in the blue polypropylene thread coincided with those of the mesh and the reinforcement, probably a result of contamination. Only antimony (Sb) was present just in the polypropylene filament (Table 2). It is worth highlighting the presence of traces of lead (Pb) in the metallic reinforcement of the endoprosthesis.

The following elements were also analysed: Li, Be, V, Ga, Ge, Xx, Sr, Y, Zr, Nb, Mo, Ru, Ag, Cd, Ix, Te, Cs, Ba, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Hf, Ta, W, Re, Os, Ti, Bi, Th and U. Their levels appeared under the detection threshold of the technique.

The endoprosthesis consisted of a self-expandable metallic mesh composed of a material with a 35°C thermo-memory. At this temperature, it unfolded or expanded up to a predefined size. The ICP-MS results were consistent with the known composition of Nitinol® (Table 2).

### Clinical evolution

The patient was kept compensated with a bearable symptomatology if she took the antihistamine (cetirizine) treatment and applied a hydrocortisone base lotion to the lesions that recurrently appeared. In view of the good control of the cutaneous vexation and the risk involved in re-intervention to withdraw the endoprosthesis, we decided to leave it. The patient died of a

Table 2. Endoprosthesis analysis. Semi-quantitative determination of metal performed with plasma-induction joint mass-spectrometry technique

| Detail composition of the stent (ppm) |      |               |               |
|---------------------------------------|------|---------------|---------------|
| Metals                                | Mesh | Reinforcement | Polypropylene |
| Al                                    | 41   | 46            | 108           |
| Ti                                    | 21%  | <1            | 68            |
| Cr                                    | 66   | <10           | 21            |
| Mn                                    | 9    | <1            | 13            |
| Fe                                    | 238  | 25            | 236           |
| Co                                    | 2    | <1            | <1            |
| Ni                                    | M    | <10           | 109           |
| Cu                                    | 286  | 15            | 315           |
| Zn                                    | <10  | <10           | 99            |
| Rh                                    | —    | 166           | —             |
| Pd                                    | —    | 55            | —             |
| Sn                                    | —    | 12            | <10           |
| Sb                                    | —    | —             | 23            |
| Ir                                    | —    | 13            | —             |
| Pt                                    | 2    | M             | 16            |
| Au                                    | —    | 19            | —             |
| Pb                                    | —    | 48            | —             |

number of laboratory register Reg. 98-067

M: elements present in great amount.

M in nickel is approximately 55% in the mesh.

M in platinum is approximately 60% in the reinforcement.

cerebrovascular hemorrhage during the last week of May 1999. She suffered a massive haemorrhagic stroke secondary to her arteriosclerotic and hypertensive pathology.

### Discussion

The discussion in this case comprises 5 aspects: (i) review of the type of cutaneous reactions provoked by metallic implants; (ii) review of the type of metals involved in these cases; (iii) discussion of the imputability of the clinical picture to the release of metal by the endoprosthesis; (iv) evaluation of the utility of preoperative epicutaneous tests; (v) to consider how to prevent and/or avoid this complication.

The clinical aspect of the eruptions associated with implants, mainly orthopaedic, can be quite varied (6), mainly adopting 2 clinical forms, one localized and another generalized. In the localized forms, the eczema develops on the skin overlying the point where the metallic prosthesis is located (7). The generalized eruptions can consist of erythema (8), urticaria (9, 10), eczema (11, 12) and, infrequently, vasculitis (13). Generalised eczema can take on a nummular or discoid form. Exceptionally, an eosinophilic cellulitis in the form of recurrent dermatitis has been described overlying a prosthetic hip (14). Eczema caused by orthopaedic prostheses is resolved by withdrawing the prostheses (15). The patient that we present showed generalized pruriginous dermatitis, distributed in plaques and with a nummular form, secondary to an endovascular implant.

Vitallium<sup>®</sup>, stainless steel and tantalum are materials widely used in prosthetic technology. These materials are characterized by being resistant to biological fluid-mediated corrosion and can be kept in the body indefinitely (16). Vitallium<sup>®</sup> is a cobalt-based alloy that contains approximately 30% chrome (Cr) and 5% molybdenum (Mo). It is perhaps the most inert prosthetic material. Stainless steel is a generic term that includes different Fe-Cr alloys. Since the Second World War, AISI 316 steel has been widely used with good results. Its failure is normally attributed to bad implantation. Steel 316 is inert for bone and tissue. It has beneficial characteristics such as strength, great resistance to fatigue, easy pliability into different forms and economical cost. The ideal prosthetic material should have the mechanical properties of steel 316 and the inert quality of Vitallium<sup>®</sup>. Tantalum is very ductile and is used as wire, suture material or mesh. Other metals or alloys used in prosthetic technology are titanium, zirconium, Elgiloy<sup>®</sup> and Ticonium. These materials have adequate resistance against body fluids, but they are

not widely used, for various reasons such as their high cost and limited clinical experience, which makes them useful for only certain specific applications. Elgiloy is used, e.g., for repairing heart valves, and, more recently, in the composition of new vascular endoprostheses. Some experimentation has also been carried out with new materials like ceramic or carbon fibre base compounds that are not so resistant to corrosion.

When we refer to dental prostheses, we know that gold (Au) has been used in different types of alloys that contain variable quantities of Au, Pt, Pd, Ag, Cu, Zn, In and Ga. Alloys of "non-precious" metals or metals with "memory" are also used. Some examples are Nitinol<sup>®</sup> (60% Ni, ~40% Ti), Elgiloy<sup>®</sup> (40% Co, 20% Cr, 15% Ni, 9% Mo, 16% Fe) or B-titanium (98% Ti, 2% Mo). The new stainless steel prostheses have compositions that always include variable quantities of Cr (16–30%), with either no Ni content or up to 70% and variable quantities of Co (60% or traces). Other materials are also included like Mn, Be, Si, Mo, W, C, Al. Because of its carcinogenic potential, beryllium (Be) is being replaced by yttrium (17).

The patient that we present developed a generalized eczematous dermatitis probably induced by the metal content of Nitinol<sup>®</sup>. This material is the main constituent of the self-expandable metallic mesh of the Vanguard<sup>®</sup> endoprosthesis used in the endoluminal repair of AAAs. The majority metallic composition of the hand-woven mesh of the stent of the endoprosthesis that we analysed is Ni (~55%) and also contains Ti (~20%) and Al (41 ppm), Cr (66 ppm), Mn (9 ppm), Fe (238 ppm), Co (2 ppm), Cu (286 ppm), Zn (<10 ppm), Pt (2 ppm). Nitinol<sup>®</sup> is characterized by having thermomemory and recovering its initial form or expanding at temperatures above 35°C. This property is used to be able to insert it into the human body through small orifices and, once it is in the correct place, in our case, inside the aorta, it expands and takes on the anatomical size of the vessel to be repaired.

The possible etiological responsibility of the Ni content of the endoprosthesis for the eczema and generalised pruritus that the patient presented is suggested by various factors: the temporal relationship between the surgical procedure and the subsequent appearance of the cutaneous problems; the clear positive result of the patch test for nickel sulfate and cobalt chloride; and the persistence of symptoms that were well controlled with treatment. Likewise, the patient got worse after angiography. We do not know exactly the cause. We speculate on the possibility of removing metal from the endograft during the procedure.

It is very difficult to confirm the responsibility

of implants in dermatitis, because the cutaneous lesions are extremely varied, generalized or localized and, besides, can develop late, even years later. It is often not possible to prove definitively such a relationship without extracting the implant. Definitive confirmation of implants' responsibility requires a pathologic study of the adjacent tissue and also a patch test using the implant itself. In this case, we should expect an inflammatory tissue reaction and a positive patch test to the implant itself. The complexity of the surgical procedure and the risks inherent in re-intervention for the patient, as well as the good response to the symptomatic treatment maintained, led us to keep the endoprosthesis in and not withdraw it to seek confirmation. Another Vanguard<sup>®</sup> endoprosthesis was used for our studies.

It has been shown that Ni can be released, e.g., from stainless steel prostheses by the action of sweat, blood and physiological saline solutions. The negative result of the dimethylglyoxime test could be explained by an incorrect laboratory reproduction of the biochemical (contact with biological fluids) and physical (mechanical and thermal) physiological conditions that the endoprosthesis is subjected to in the interior of the human body. In studies carried out with laboratory animals, it was possible to detect Ni in the tissue adjacent to the implant. One of the objectives of scientists responsible for creating new implants, in order to avoid eczema reactions, is to reduce the production of the metallic particles caused by use, rubbing or corrosion.

Furthermore, studies of nickel release from such endoprosthesis in direct and prolonged contact with different solutions and body fluids, must be carried out in the future.

The potential of sensitization to an implanted metal that constitutes an alloy has been retrospectively and prospectively assessed. The meaning of this type of study is difficult to interpret, particularly because allergy to contact with metals is a frequent phenomenon in the general population.

There exist no totally sure methods for detecting individuals who are susceptible to suffering this type of cutaneous complication when planning to implant a prosthesis or endoprosthesis. The specificity and sensitivity of the patch test is insufficient. The need to perform pre-surgical patch tests for metals is debatable. In orthopaedic surgery, clinics usually question the safety of stainless steel prostheses applied to patients with proven contact allergy to nickel sulfate. General thought has it that the use of this type of prosthesis is not contraindicated for such patients. The failure of orthopaedic prostheses is not usually due to metal allergy. In orthopaedic surgery, it can be said that stainless

steel prostheses can safely be used for patients who are allergic to Co, and prostheses of Vitallium<sup>®</sup> for patients allergic to Ni, without systematically specifying Ti implants for those in whom allergic reactions have not been described.

There has not been enough experience to be able to predict what prevalence this type of complication will have in endoluminal surgery. We believe that, due to the older age and the sex, mainly men, of the patients who are susceptible to being operated on with this technique, it will not be high.

Nevertheless, surgeons should be cognisant of this type of cutaneous complication and the metallic composition of the implants they handle. We recommend that this clinical aspect be taken into account in patients' anamneses before any surgical procedure that requires implanting either a prosthesis or an endoprosthesis. The choice of the most adequate prosthetic material and knowledge of the patient's pathological antecedents will make it possible to prevent an eventual cutaneous complication.

To conclude, we can state that we have witnessed a case of disseminated generalized eczema probably or possible due to the Ni content of Nitinol<sup>®</sup> and released into the blood. Nitinol<sup>®</sup> is the main material in the make-up of the metallic mesh of the Vanguard<sup>®</sup> endoprosthesis used for the endoluminal repair of the abdominal aorta aneurysm that we were dealing with. It is recommended that patients' pathological antecedents for allergies be taken into account in preoperative questioning. Probably, the design of new endoprostheses inserting an internally covered metallic self-expandable stent may prevent eczematous reactions which, albeit infrequent, can be caused by the implantation of a vascular endoprosthesis.

### Acknowledgement

We thank Dr. Lacort of the Elemental and Molecular Analysis Section of the Universitat de Barcelona for her collaboration in the analysis of metals.

### References

1. Akkersdijk G J M, Van der Graaf Y, Moll F L, De Vries A C, Kitslaar P J E H M, Van Bockel J H, Hak E, Eikelboom B C. Complications of standard elective abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg* 1998; 15: 505-510.
2. Parodi J C, Palmaz J C, Barone H D. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg* 1991; 5: 491-499.
3. Volodos N L, Karpovich I P, Troyan V I, Kalashnikova Yu V, Shekhanin V E, Ternyuk N E, Neoneta A S, Ustinov N I, Yakovenko L F. Clinical experience of the use of self-fixing synthetic prostheses for remote endoprosthetics of

- the thoracic and in the abdominal aorta and iliac arteries through the femoral artery and as intraoperative endoprostheses for aorta reconstruction. *Vasa* 1991; 33: 93-95.
4. Dermatitis from metals used in medical devices and implants. In: Rietschel R L, Fowler J F. *Fisher's contact dermatitis*, 4th edition. Baltimore: Williams & Wilkins, 1995: 414-447.
  5. Giménez Arnau A. Dermatitis ocasionada por metales utilizados en tecnología médicoquirúrgica. *Actual Dermatol* 1999; 38: 379-394.
  6. Kubba R, Taylor J S, Marks K E. Cutaneous complications of orthopedic implants. *Arch Dermatol* 1981; 117: 554-560.
  7. Cramers M, Lucht U. Metal sensitivity in patients treated for tibial fractures with plates stainless steel. *Acta Orthop Scand* 1977; 48: 245-249.
  8. Ridley C M. How relevant is cobalt sensitivity in a patient with unsatisfactory total knee replacement? *Clin Exp Dermatol* 1977; 2: 401-404.
  9. Symeonides P P, Paschaloglou C, Papageorgiou S. An allergic reaction after fixation of a fracture using a vitallium plate. *J Allergy Clin Immunol* 1993; 51: 251-252.
  10. McKenzie A W, Aitken C V E, Ridsdill-Smith R. Urticaria after insertion of Smith-Petersen Vitallium nail. *Br Med J* 1967; 4: 36.
  11. Pegun JS. Nickel allergy. *Lancet* 1974; 1: 674.
  12. Meyrick-Thomas R, Rademaker M, Goddard N J, Munro D D. Severe eczema of the bands due to an orthopaedic plate made of vitallium. *Br Med J* 1987; 294: 106-107.
  13. Munro-Ashman D, Miller A J. Rejection of metal to metal prosthesis and skin sensitivity to cobalt. *Contact Dermatitis* 1976; 2: 65-67.
  14. Stierstorfer M B, Clendenning W E. Recurrent dermatitis overlying a prosthetic hip. Eosinophilic cellulitis (Wells« syndrome). *Arch Dermatol* 1991; 127: 1397-1398.
  15. Carboni G P, Contri P, Pilla G, Vasina P G. Dermatitis associated with orthopaedic prostheses and internal fixations. *Contact Dermatitis* 1994; 31: 197-198.
  16. Ludwigson D C. Today's prosthetic metals. *J Metals* 1964; March 1.
  17. Vilaplana J, Romaguera C, Cornellana F. Contact Dermatitis and adverse oral mucous membrane reactions related to the use of dental prostheses. *Contact Dermatitis* 1994; 30: 80-84.
  18. Fisher A A. The safety of stainless hip prosthesis in nickel-sensitive individuals. *Cutis* 1993; 52: 193.
  19. Lalor P A, Gray A B, Wright S, Railton G T, Freeman M A, Revell P A. Contact sensitivity to titanium in hip prosthesis? *Contact Dermatitis* 1990; 23: 193-194.

Address:

Ana Giménez-Arnau  
Dermatología  
Hospital del Mar  
Passeig Marítim 25-29  
08003 Barcelona  
Spain