CONTACT ENDOSCOPIC FINDINGS IN HEREDITARY HEMORRHAGIC TELANGIECTASIA

Urban W. Geisthoff, MD, Christian Sittel, MD, Peter K. Plinkert, MD

Department of Otorhinolaryngology, University Hospital of the Saarland, Univ.-HNO-Klinik, Kirrberger Str., D-66421 Homburg, Germany. E-mail: urban.geisthoff@uniklinik-saarland.de

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Abstract:  Background. Hereditary hemorrhagic telangiectasia is characterized by angiodysplastic lesions. So far, knowledge is limited on the vascular architecture and rate of occult manifestation of telangiectases. Contact endoscopy has not been used for this task before.

Methods. Eleven patients with hereditary hemorrhagic telangiectasia were examined with contact endoscopy to identify occult telangiectases. Sixty enoral telangiectases were studied in detail to characterize their architecture.

Results. No occult telangiectases could be detected. In most cases, telangiectases consisting of a simple dilated loop were small. In contrast, most of the complex telangiectases were larger.

Conclusions. Visually normal areas in patients with hereditary hemorrhagic telangiectasia did not seem to have abnormal vascularization. Simple dilated capillary loops might be precursors of telangiectases with a more complex structure. Contact endoscopy seems to be a promising tool for the in vivo monitoring of therapies and the natural course of vascular disorders in humans and in animal models.

Keywords:  hereditary hemorrhagic telangiectasia; contact endoscopy; Rendu-Osler-Weber disease; angioarchitecture; in vivo

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal dominant disorder with age-related penetrance. The disorder is characterized by vascular anomalies that may develop in virtually any organ. The prevalence varies and may approach one in 10,000 in specific regions. Linkage studies have identified at least three HHT loci on chromosomes 9 and 12; a third locus is postulated. A combined syndrome of juvenile polyposis and HHT has been identified recently. The mutated genes on chromosome 9 and 12 encode respectively for endoglin and activin receptor-like kinase 1. Both proteins are involved in the transforming growth factor (TGF)-β pathway and play a role in angiogenesis and vessel maturation. They are also part of an interplay between cells, matrix, and external factors in responding to vascular insults. Normal angiogenesis has been separated into two phases. The initial phase involves endothelial cell migration and vessel formation; the second phase encompasses small vessel enlargement by expansion. The development of abnormal vessels in HHT resembles this second phase,
and it has been suggested that HHT is a reason-
able model for this phase.8,9 Clinical manifesta-
tion of HHT includes recurrent epistaxis, easily
bleeding mucocutaneous telangiectases (TAEs),
and larger arteriovenous malformations (AVMs)
in parenchymatous organs like lungs, liver, and
brain, with liver involvement being the most com-
mon visceral manifestation.10 Pulmonary AVMs
are significant risk factors because of their as-
association with paradoxical, sometimes septic,
emboli. A rare but equally serious threat is he-
moptyis or hemothorax. These potentially fatal
complications are the rationale for early diagno-
sis.5,7 At present, a diagnosis based on genetic
analysis is impossible for some families. A defi-
nite clinical diagnosis of HHT is based on family
history and the presence of TAEs or AVMs. Al-
though TAEs are the hallmark of the disorder,
they usually do not appear earlier than in the
third decade of life, may be subtle, and are
sometimes difficult to distinguish from cherry
angiomias or venectasia.1,8,11 In 2000, the Sci-
entific Advisory Board of the HHT Foundation In-
ternational Inc. published a consensus about
the clinical diagnosis of HHT.12 One of four crite-
ria is the presence of multiple TAEs at charac-
teristic sites including the lips, oral cavity, fingers,
and nose. No general agreement exists on the
usefulness of screening for AVMs in doubtful
cases. Capillary microscopy of the nail fold proved
to be a valuable tool in detecting microscopic
vascular dilatations if no typical TAEs have been
detected by routine inspection.13 In 1995, the
Dutch group around Cornelius Westermann pub-
lished its own results and a review about the
distribution of TAEs.14 According to their data,
TAE could be found at the extremities in 31% of
patients. The findings in percent for nasal mucosa
(83%), face (33%), oral mucosa and lips (67%) are
higher, for conjunctiva (22%) lower. They found
their data to be consistent with most other pub-
llications. Therefore, examination of these sites by
contact endoscopy seems to be promising for detec-
tion of microscopic TAEs.

For contact endoscopy the objective lens is
directly applied to the tissue, so that, similar to
immersion microscopy, only a thin liquid film in
between remains. Cells of superficial tissue layers
can be visualized in vivo and in situ natively or
after staining with methylene blue with magnifi-
cations up to 150×. Especially attractive is the
possibility to use this technique to study the fine
structure of tissues located in cavities where the
use of a microscope is impractical, like the uter-
us.15 In most clinical applications, contact endos-
copy has been used to analyze tissue dignity (eg,
to assess laryngeal cancer and its preceding
lesions).16 Another indication is the identification
of tissue like the parathyroid in thyroid oper-
ations.17,18 Mario Andrea and coworkers used
contact endoscopy to examine stained superficial
cell layers of the nasal mucosa,18 but they already
noticed the possibility of identifying the mucosal
microvascular network including the circulating
blood cells. To the best of our knowledge, no re-
ports on contact endoscopic findings in HHT exist.
Therefore, we decided to evaluate the value of
this technique for the diagnosis of HHT and in
the in vivo examination of TAEs.

MATERIALS AND METHODS

Procedure. Initially, the feasibility of contact
doscopy of the oral, nasal, conjunctival mucosa,
and the facial skin was evaluated in two healthy
subjects. Visibility of normal vascular structures
was best in the mucosa of the lateral oral cavity.
Therefore, after obtaining informed consent, con-
secutive patients undergoing treatment for HHT
at our institution were enrolled in the study. In
addition, patients with TAE of the nasal mucosa,
skin, and conjunctivae were asked to be part of
an investigation of these regions. TAEs were de-
defined as “circumscript superficial dilated vascular
structures.” Circumscript means that no normal,
stretched, larger superficial vessels are counted.
A lesion was regarded as superficial if at least
a part of it lay in the depth of surrounding capil-
ary loops. The maximum vessel diameter of
this part of the lesion had to be at least three
times the size of the maximum diameter of sur-
rounding capillaries. One investigator (UWG) per-
formed all examinations.

Patients and Sites Studied. We studied a random
sample of 11 patients (seven women and four
men) who had a definite clinical diagnosis of HHT
according to the Curacao criteria.12 The mean age
of the patients was 48 years (range, 22–66 years).
We investigated the buccal mucosa of all pa-
tients for a minimum of 5 minutes each to search
for occult angiodysplasia. These examinations
were performed in a meandering pattern scanning
a minimum of 3-cm × 2-cm mucosal surface area
each. Sixty enoral telangiectatic lesions being eas-
ily accessible were studied in detail.

In addition, in six patients, the nasal mucosa
was studied, in three the conjunctival muco-
Technical Equipment. We used a 0° contact endoscope (type 8715 AA, diameter 5.5 mm, 80° field of view, Karl Storz, Tuttingen, Germany) in the 60× amplification mode in combination with a three-chip endoscope camera and a xenon light source. Examinations were documented on digital videotape.

RESULTS

Practical Aspects. The practical aspects of the different examination sites were assessed subjectively by the investigator (UWG) in two healthy subjects. These results were confirmed and completed after gaining further experience with the method during the examinations of patients with HHT. They are listed in Table 1. On the basis of this experience, we decided to choose the examination of the buccal mucosa as the standard method in searching for occult TAE.

Figure 1 shows a typical finding of normal mucosa of the cheek. In analogy to the vascular structure of the outer dermis, three different layers can be differentiated: (1) superficial capillary loops standing orthogonal on a (2) horizontal plexus that is connected to deeper vascular structures by (3) an ascending arteriole and an accompanying venule. If inspected from an orthogonal direction, a capillary loop sometimes appeared by summation effects like a angiodysplasia. Stretching of the capillary loop structure by slight movements of the endoscope was useful in avoiding these summation effects.

Air bubbles (Figures 2 and 3) and debris could reduce the quality of visualization. The amount of pressure when applying the endoscope to the tissue is of paramount importance. Insufficient pressure will result in a loss of contact. High pressure expels all blood from the vessels, making them practically invisible so that even large TAE may be neglected. Ideal pressure will reduce the background red color enhancing contrast between vessels and the surrounding tissue. A slight increase of pressure reduces the microvascular blood cell velocity allowing determination of its direction, so that feeding and draining vessels can be distinguished. Interpretation was sometimes difficult, because inhomogeneous application of pressure was able to invert the flow direction in parts of complex telangiectatic lesions (Figure 4).

Search for Occult Telangiectasia. No occult TAEs that were invisible to the naked eye could be detected by contact endoscopy enorally, endonasally, in the region of the conjunctivae or on the outer skin.

In the region of the buccal mucosa, some macroscopic visible red maculae suspected of being TAE were shown to be hematomas and not vascular structures.

Architecture of Enoral Telangiectasis. Sixty-one enoral vascular lesions from 11 patients were studied thoroughly. In all but one lesion, the typical changes compared with normal vessels

<table>
<thead>
<tr>
<th>Examination site (no. of patients examined)</th>
<th>Accessibility, applicability, and patient tolerance</th>
<th>Visualization</th>
<th>Probability of telangiectases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoral: tongue (3)</td>
<td>Medium (caused by movements of the tongue)</td>
<td>Fair (papillae)</td>
<td>High</td>
</tr>
<tr>
<td>Enoral: floor of mouth (3)</td>
<td>Good</td>
<td>Good</td>
<td>Low</td>
</tr>
<tr>
<td>Enoral: cheeks (11)</td>
<td>Good</td>
<td>Very good</td>
<td>Medium</td>
</tr>
<tr>
<td>Endonasal (4)</td>
<td>Medium (sensitive area, bony, or cartilaginous submucosal tissue, induction of bleeding in 2 patients, 30° endoscope probably advantageous)</td>
<td>Fair (crusts, nasal ointment)</td>
<td>Medium</td>
</tr>
<tr>
<td>Conjunctival mucosa (3)</td>
<td>Medium (sensitive area with resulting movement of the patient)</td>
<td>Fair (caused by movements of the patient?)</td>
<td>Medium</td>
</tr>
<tr>
<td>Skin (5× facial skin including lips, 1× fingertips)</td>
<td>Good</td>
<td>Bad (squamated epithelium)</td>
<td>High</td>
</tr>
</tbody>
</table>
consisted of dilatation of superficial vessels. In the exception mentioned, a nidus of multiple intertwined vessels of a diameter similar to normal capillaries was observed (Figure 2). After consultation with a pathologist, the lesion was interpreted as capillary hemangioma not related to HHT.

The other 60 vascular lesions could be divided into two groups according to their architecture. Simple TAE consisted of a single dilated vessel loop (Figure 3). In contrast to the classification of pulmonary AVMs,19 most of the simple TAE probably had multiple small feeding and draining vessels. It was very difficult to determine the exact number of feeding and draining vessels. These small structures lay quite deep and were often covered by the relatively large TAE. By use of endoscope movements, it was sometimes possible to push the overlying TAE aside. In some cases, careful application of pressure expelled the blood from the overlying TAE but still allowed sight of the deep smaller feeding and draining vessels. Because it was not possible to determine the number of these vessels reliably, we did not use this parameter for our attempt at a classification. Contrary to simple TAE, complex ones consisted of dilated vascular structures connected by branching in various forms (Figures 4–6). Larger complex TAEs often had the aspect of a “caput medusae” (Figure 6) or of a conglomeration of simple TAE. For the same reasons as for the simple TAE, it was sometimes difficult to determine whether ectatic vascular structures were connected by capillaries of normal diameter or by dilated vessels. The lesion was counted as being complex as soon as the first dilated branching was spotted. This was possible in most lesions consisting of more then one dilated loop.

TAEs were also classified by size of their maximum diameter in relation to the field of view: small (less then one half of the field of view), medium (1/2 to 1/1 field of view), and large (1/1 field of view and more). The diameter of the field of view is depth-dependent because of the opening angle of 80°. For TAEs of the oral mucosa, we calculated a field of view diameter of 2 to 3 mm. Very large TAE were not studied, because their visualization was shown to be very difficult. No overview of the entire malformation was possible, and if single vessel diameters were too large, overlying vessels could not be differentiated suf-
FIGURE 3. (A–D) Contact endoscopic views of small telangiectases (TAE) of simple architecture signifying that they have no dilated branching point. The flow within the TAE can be visualized by variation of the pressure applied by the endoscope. Flow speed can be reduced so that it becomes visible to the naked eye. The flow direction of this TAE is marked by an arrow (the direction of the smaller one in (C) and (D) could not be determined. Also visible are not dilated, normal capillary loops (1) and an air bubble (2) as an example of the conditions aggravating the examination. (C) and (D) are of a special interest, because two TAEs are directly next to each other although we could not detect a pathologic vascular dilatation between both.

FIGURE 4. (A, B) Medium complex telangiectasis (TAE) next to normal capillary loops (1). Flow directions are indicated by arrows. The flow direction of one vessel connected to the TAE could not be determined for sure (2). By changing application pressure of the contact endoscope, the flow direction could be inverted in point 3. In point 4, blood from a feeding supply vessel from the depth enters the TAE. It is striking that only one venous drainage could be detected for sure.
iciently when compressed. Table 2 shows the relationship of size and type of architecture.

Visualization of TAE was worse for endonasal compared with enoral lesions (Table 1). As far as we could assess, the architecture of endonasal lesions was not principally different from enoral TAE.

DISCUSSION

Contact endoscopy showed to be excellent for the in vivo visualization of the mucosal microvasculature, allowing differentiation of lesion types and detection of the blood flow direction. In contrast to capillary microscopy and capillaroscopy, contact endoscopy can also be applied inside cavities like nose and mouth. Difficulties encountered during the examination of sensitive areas like involuntary movements or induc-

Table 2. Relationship of size and type of architecture of 60 telangiectases of the buccal mucosa.

<table>
<thead>
<tr>
<th>Size</th>
<th>Simple</th>
<th>Complex</th>
<th>Not clear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>8</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Medium</td>
<td>1</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Large</td>
<td>0</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
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tion of bleeding in the nose might be reduced by the use of local or general anesthesia. Especially for the nasal examination, the use of an angled endoscope and cleaning of the examined site by irrigations are probably helpful. Potential future applications of mucosal contact endoscopy in HHT or other vascular disorders are in vivo monitoring of the natural course of the disease and of the therapeutic effects of drugs on the disorder and to study hemodynamics and the correlation of the vascular phenotype with the genotype in humans or in animal models.

Examination of the squamous epithelium of the skin was shown to be insufficient because of deficient visualization quality.

Like in vivo Doppler, optical coherence tomography examination by contact endoscopy did not reveal occult TAEs. The diagnostic value in HHT is, therefore, limited to the differentiation of TAEs from other maculae. Until now, occult abnormal vessels have only been detected by capillary microscopy of the nail fold.

Braverman et al studied the size-dependent three-dimensional architecture of 10 cutaneous TAEs in HHT by light and electron microscopy. Pinpoint lesions had a focal dilatation of post-capillary venules. As the lesions enlarged, arterioles became dilated, followed by dramatic venular dilatation. These dilated postcapillary venules are believed to eventually bypass the capillary networks and fuse directly with dilated arterioles, forming direct arteriolar–venular communications and large TAE. This thesis has been supported by the capillary microscopic findings of the nail fold. In five cases, giant loops were found between normal capillary loops. In only two cases, the draining limb was dilated, which might be the precursor of the giant loop. We also found dilated capillary loops similar to the giant loops photographed by capillary microscopy, which also have been found in hereditary benign telangiectasia, but we did not find exclusive dilatations of the draining limb. We called these lesions “simple” in contrast to “complex” TAEs, including branchings of dilated vascular structures. Presuming all TAEs have a tendency to grow, our data suggest these simple TAEs are precursors of complex ones. In this case, it would be interesting to know if branching occurs by extension of the dilatation from the capillary loop onto the horizontal plexus and from there onto other capillary loops or if the branchings are a consequence of angiogenesis. The detection of superficial (Figures 4 and 5) and quite deep branchings (Figure 6) supports both theories. Another possibility is that simple and complex TAE are different lines of development and that the simple ones stay relatively small, whereas complex TAEs are more probable to grow. Simple independent TAEs as probably visible in Figure 3c and 3d might also form complex ones by junction. It is thought that large AVMs may arise from microscopic lesions by a process of remodeling. Therefore, it is interesting that a similar classification has been introduced by White et al for pulmonary AVMs. Simple pulmonary AVMs consist of a single feeding pulmonary branch connecting it to a bulbous, aneurysmal, nonseptal communication with a single draining vein. In the complex type, two or more pulmonary artery branches are connected to a cirsoid aneurysmal, septated communication with two or more draining veins. White and coworkers are discussing an older theory assuming that all pulmonary AVMs begin as a plexus-type connection and later might differentiate to a simple AVM. White et al observed that several small pulmonary AVMs were of the simple type and therefore proposed that the forerunners are of the same type as the fully developed forms. As mentioned previously, the natural development of TAEs might be monitored during longitudinal studies by contact endoscopy to answer these questions. In this study, mainly the angioarchitecture of enoral lesions was analyzed. We could not detect striking differences compared with TAEs of other regions studied, which, for example, might explain the bleeding tendency of nasal TAE. To search for slight structural or quantitative differences, further examinations under optimized conditions like anesthesia seem to be interesting.

One vascular lesion detected by contact endoscopy probably was a small capillary hemangioma. Interestingly, the lesion resembles cerebral vascular malformations also found in patients with HHT and a murine HHT model. The implication of this observation is not clear. In the same murine HHT model, arterioles with a relative constriction of the branching points were described, which also could not be detected in mucocutaneous TAEs by our examination technique.

**CONCLUSIONS**

Contact endoscopy allows excellent visualization of mucosal TAEs in HHT. Our data suggest that small enoral TAEs with a simple architecture precede larger ones with branchings of the dilated structures. No occult TAE could be detected. The
technique seems to be suitable for the in vivo monitoring of microvascular changes because of therapies or the natural course in disorders and to study hemodynamics and the correlation of the vascular phenotype with the genotype in humans or in animal models.

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